Cu/Fe-Catalyzed C-C, C-N and C-S Cross-Coupling Reactions: Synthesis of Biologically Important Heterocycles

Thesis submitted to

National Institute of Technology, Rourkela

for the degree of

DOCTOR OF PHILOSOPHY

By

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... Dedicated to my parents

“Great things are not done by impulse,
But by a series of small things brought together”

Vincent van Gough

CERTIFICATE

Dr. Niranjan Panda
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This is to certify that the thesis entitled "**Cu/Fe-Catalyzed C-C, C-N and C-S Cross-Coupling Reactions: Synthesis of Biologically Important Heterocycles**" being submitted by Ashis Kumar Jena, to the National Institute of Technology, Rourkela, India, for the award of the degree of **Doctor of Philosophy** is a record of bonafide research carried out by him under my supervision. I am satisfied that the thesis has reached the standard fulfilling the requirements of the regulations relating to the nature of the degree. The contents of the thesis have not been submitted to any other university or institute for the award of any degree or diploma.

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Acknowledgments

First of all, I would like to express my profound gratitude to my supervisor Prof. Niranjan Panda for his excellent guidance, constant encouragement, continuous support and inspiration during the entire period of my research work. I am highly indebted to him for giving me enough freedom to explore my scientific work in a new direction. I would believe myself really fortunate to be associated with him at the important turn of my carrier.

I wish to express my sincere thanks to Prof. Sasmita Mohapatra for her valuable guidance and contribution to my scientific work at the time of requirement.

I am thankful to Prof. N. Panda, Head of the Chemistry Department and Prof B. G. Mishra, Prof. R. K. Patel (Ex-head, Department of Chemistry) for providing me the departmental facilities to make this programme success.

I am grateful to Prof. M. Equeenuddin, Department of Mining Engineering and Prof. Kakoli Karar(Paul), Department of Civil Engineering for Atomic Absorption Spectroscopy. I am thankful to Mr. Uday Sahu, Department of Metallurgical and Materials Engineering for Powder X-Ray Diffraction studies and Mr. Rajesh Pattnaik, Department of Metallurgical and Materials Engineering for Scanning Electron Microscopy.

I wish to place on record my thankfulness to numerous technical and non-technical staffs of chemistry department, NIT, Rourkela who have lent their expertise and cooperation at various stages of this endeavor. I am thankful to Mr. Samir Kumar Patra, laboratory assistant, chemistry department, for his help.

Special thanks to my friend Swagatika Sahu for her help and support during this programme.

I am very much fortunate to have friendly, helpful and supportive colleagues in my laboratory. It is a great pleasure for me to thank all my lab mates Soumi Karmakar, Raghavender Mothkuri, Smruti Ranjan Rout, Dinesh Kumar Nayak, Krushna Chandra

Acknowledgments

Sahoo, Hrushikesh Sahoo, Swapna Mohapatra, Archana Kumari, Vasundhara Thakur, Arpan Pal for their kind support and help during my research work. I thanks to summer internship students like Vivekananda, Rahul Kumar Das, Parikhit Padhke for their cooperation.

I am grateful to my family members for their support and encouragement. Particularly, my deepest sense of gratitude goes to my parents, Mr. Suresh Chandra Jena and Mrs. Urmila Jena, my sister and my brother in law for their constant encouragement, unconditional support and endless love for this academic pursuit.

I am indebted to National Institute of Technology, Rourkela for the award of Institute Fellowship.

I thanks to the Director, National Institute of Technology, Rourkela for providing outstanding facilities and allowing me to present this work in the form of a thesis.

Finally, I wish to thank all of my friends for making my stay in this institute a memorable one.

Date:

NIT Rourkela **Ashis Kumar Jena**

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Biography

Mr. Ashis Kumar Jena was born at Athgarh (Cuttack), Odisha on 26th Jun, 1985. He has received Bachelor of Science with honours in chemistry from Gopabandhu Science College, Athgarh, Utkal University in 2006, scoring highest percentage of marks in honours. He was then awarded with *Post-Graduate Merit Scholarship* (2006-2008) for university rank holders by MHRD, India and continuing his Master of Science in chemistry at Utkal University, Odisha. He successfully completed the M.Sc. programme in 2008 from the same university. In the same year, he qualified Graduate Aptitude Test for Engineering as well as National Eligibility Test for Lectureship conducted by Council of Scientific and Industrial Research, India. In 2009, he joined at the Department of Chemistry, National Institute of Technology, Rourkela, as a research scholar with the award of *Institute fellowship* (2009-2013). During his doctoral programme, he has published the scientific work in many international journals, which mainly include *Journal of Organic Chemistry, ACS Catalysis, Applied Catalysis A: General, Tetrahedron Letters, Chemistry Letters and Chemistry of Heterocyclic Compound*. He also attended various national and international symposium, conference etc.

His area of interest includes synthetic organic chemistry, organometallic chemistry and heterocyclic chemistry.

Abstract

Cross-coupling reactions are an important methodology for the formation of various types of carbon-carbon and carbon-heteroatom bonds. Now a days these reactions are applied in a variety of synthetic venues starting from total synthesis of natural and non-natural products to pharmaceutically important molecules and functional materials. The coupling reactions are generally carried out by using a range of transition-metals including Ru, Rh, Pd, Pt, Au, Ni etc. However, the high cost, toxicity of TM and use of ancillary ligands often restrict their utility in organic reactions. Thus, researchers have turned their attention towards the use of less expensive and environment friendly catalyst for the C-C and C-hetero bond forming reactions. Indeed, Cu/Fe-catalyzed cross-coupling reactions have gained much attention owing to the low cost and environmental friendly nature of Cu/Fe catalysts. Indeed, significant progress has been made on the use of homogeneous Cu/Fe catalysts in organic synthesis. However, homogeneous catalysis suffers from the problematic separation of the catalyst for reuse. Furthermore, the homogeneous catalysts tend to lose their catalytic activity because of aggregation of the metal catalyst. To circumvent the aforementioned problems, several heterogeneous catalytic systems for cross-coupling reactions have been developed. In recent years, the catalytic activity of nanoparticles in organic transformations has been exploited owing to their high surface area. However, the small size of the nanoparticles, renders the incomplete separation of the catalyst from the reaction medium. To make the separation process simple and efficient with retention of catalytic activity, magnetic nanoparticles are the attractive solution. In this context, our detailed efforts on the development of cost effective Cu/Fe-based catalyst systems for C-C and C-hetero bond forming reactions and their applications in the synthesis of biologically important heterocycles have been described in this thesis.

The present thesis entitled **"*Cu/Fe-Catalyzed C-C, C-N and C-S Cross-Coupling Reactions: Synthesis of Biologically Important Heterocycles*"** is divided into five chapters.

Chapter 1 contains a brief overview about the Cu/Fe-catalyzed carbon-carbon and carbon-heteroatom cross-coupling reactions. The objective of our present work to meet some of the challenges associated with the C-C and C-hetero cross-coupling reactions are also presented.

Abstract

Chapter 2 deals with the coupling of terminal alkynes with aryl halides in presence of magnetic copper ferrite nanoparticles. The separation of the catalysts using external magnet for successive reuse in Sonagashira-type coupling reaction has been described in detail.

Chapter 3 describes the N-arylation of various nitrogen containing heterocycles with aryl halides using copper ferrite nanoparticles under ligand-free conditions. A range of aryl halides including aryl bromides and chlorides were successfully used as the coupling partner for the C-N cross-coupling reactions.

Chapter 4 deals with the C-S cross-coupling reactions between thiols and aryl halides. The scope of the tandem C-S/C-N cross-coupling reactions has been exploited for the synthesis of biologically important dibenzothiazepine derivatives.

Chapter 5 demonstrates an expedite synthesis of substituted pyrazoles from diarylhydrazones and vicinal diols employing cheap and environmental friendly iron catalyst. This protocol is practical and highly regioselective to synthesize a number of 1,3 and 1,3,5 substituted pyrazoles in 51-85% yield.

General Details

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out in flame-dried flasks under nitrogen atmosphere. Solvents and reagents were dried and purified by distillation before use as follows: Tetrahydrofuran (THF), benzene, toluene, xylene and diethyl ether (Et_2O) from sodium benzophenone ketyl; dichloromethane (CH_2Cl_2), carbon tetrachloride (CCl_4) and acetonitrile (CH_3CN) from P_2O_5; DMSO and DMF from CaH_2; Et_3N, pyridine, and diisopropylamine from solid KOH; and methanol from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (particle size 100-200 mesh, 60-120 mesh, SRL India) using ethyl acetate and petroleum ether (60-80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plate (silica gel GF 254 and silica gel G, Merck). ^1H NMR and ^{13}C NMR were recorded on Bruker Advance 400 MHz spectrometers using $CDCl_3$ and mixture of $CDCl_3$ and DMSO-d_6 as solvent and in some cases DMSO-d_6. Tetramethylsilane (TMS) was used as internal standard (0.0 ppm). Chemical shifts are reported in ppm downfield (δ) from Me_4Si. Coupling constant (J value) were given in Hz. The abbreviation used for ^1H- and ^{13}C-NMR multiplicities follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd) and broad singlet (bs). IR Spectra were recorded on KBr pellets or in dichloromethane on Perkin Elmer Spectrophotometer. IR bands are expressed in frequency (cm^{-1}). Plastic coated magnetic rod is used as magnetic separator for separation of catalyst. AAS were analysed by Perkin Elmer A Analyst 200 Spectrometer.

Abbreviations

Acetonitrile	CH_3CN
Acetyl acetone	acac
Aluminium oxide	Al_2O_3
Ammonia	NH_3
Benzotriazole	BtH
Cesium Carbonate	Cs_2CO_3
Copper	Cu
Cobalt ferrite	$CoFe_2O_4$
Copper acetate	$Cu(OAc)_2$
Copper acetylacetonate	$Cu(acac)_2$
Copper ferrite	$CuFe_2O_4$
Copper fluoroapatite	CuFAP
Copper Iodide	CuI
Copper oxide	CuO
Copper triflate	$Cu(OTf)_2$
Copper(**I**) thiophene-2-carboxylate	CuTC
Cuprous chloride	CuCl
Cupric chloride	$CuCl_2$
Deutaratedchloroform	$CDCl_3$
1,4-diazabicyclo[2.2.2]octane	DABCO

Abbreviations

Dibenzoyl Methane	DBM
Dichloromethane	DCM
Diethylether	Et_2O
N,N´-Dimethylethylenediamine	DMEDA
Dimethoxyethane	DME
Diphenyl pyrrolidine-2-phosphonate	DPP
Dimethyl Sulfoxide.	DMSO
N,N-Dimethylformamide	DMF
1-butyl-3-methylimidazolium hexafluorophosphate	$[bmim]PF_6$
Ethyl acetoactate	EAA
Ferric bromide	$FeBr_3$
Ferric Chloride	$FeCl_3$
Ferric acetylacetonate	$Fe(acac)_3$
Hexamethyltetraamine	HMTA
Infrared	IR
Iron	Fe
Isopropanol	$^{i}PrOH$
Lithium aluminium hydride	$LiAlH_4$
Lithium methoxide	LiOMe
Melting point	MP

Abbreviations

Microwave	MW
Nickel ferrite	$NiFe_2O_4$
N-methylpyrrolidone	NMP
Palladium acetate	$Pd(OAc)_2$
1,10-Phenanthroline	1,10-Phen.
Potasium acetate	KOAc
Potasium bromide	KBr
Potasium Carbonate	K_2CO_3
Polyethylene glycol	PEG
Potasium hydroxide	KOH
Potasium iodide	KI
Potasium phosphate	K_3PO_4
Potasium tertiarybutoxide	^tBuOK
Room temperature	rt
Sodium	Na
Sodium bicarbonate	$NaHCO_3$
Sodium carbonate	Na_2CO_3
Sodium Chloride	NaCl
Sodium sulfite	Na_2SO_3
Sodium sulfate	Na_2SO_4

Abbreviations

Sodium tertiarybutoxide	^{t}BuONa
Tetrabutylammonium bromide	TBAB
Tertiarybutylhydroperoxide	TBHP
Tetrahydrofuran	THF
TetraButylAmmoniumAcetate	TBAA
TetraButylAmmoniumhydroxide	TBAH
Thiamyl acetate	THA
Transition-Metal	TM
Triethylamine	Et_3N
Triphenylphosphine	PPh_3
N,N,N´,N´-TetramethylEthyleneDiAmine	TMEDA
Ultraviolet	UV
Water	H_2O

Table of Contents

Chapter 1

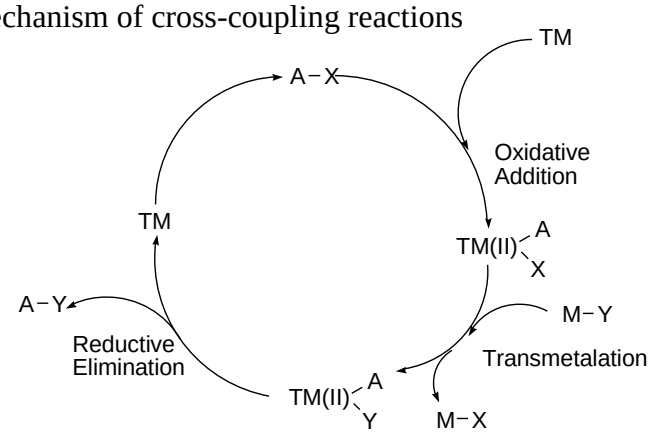
Cu/Fe-catalyzed cross-coupling reactions: A brief overview

1.1. Coupling reactions

Recently, transition-metal (TM) catalyzed carbon-carbon and carbon-hetero bond forming reactions have received paramount attention[1] because of their manifold application in academics and industries. Historically, the metal-catalyzed C-C bond forming reaction was developed by Glaser about 150 years back[2], which includes the oxidative dimerization of terminal acetylenes in presence of stoichiometric amount of copper. At the beginning of 20th century (1901), Ullmann discovered a copper-mediated synthesis of biaryls from the coupling of activated aryl bromides.[3] Subsequently, the scope of the above mentioned method has been extended towards the synthesis of diarylamines,[4] diaryl- ethers[5], though, stoichiometric amount of copper salt and high reaction temperature are needed for such transformations. The synthesis of acetaldehydes by palladium-catalyzed Wacker oxidation of ethylene, discovered in 1956,[6] probably the first Pd-catalyzed reaction, which revolutionized the chemical synthesis. Then after, a number of carbon-carbon and carbon-hetero coupling reactions were developed. Undoubtedly, these coupling reactions boost a new direction for the synthesis of organic molecules. Depending upon the nature of reactants, coupling reactions are broadly classified into two types: (a) homo-coupling reactions and (b) cross-coupling reactions. When two identical reactants couple with each other with the aid of a metal, the reaction is termed as homo-coupling reactions whereas; coupling of two different reactants in the presence of metal is called cross-coupling reactions. Generally the latter refers to a series of transformations in which an organic nucleophile reacts with an aryl, vinyl, or alkyl halides or pseudohalides in presence of a transition-metal catalyst, leading to the formation of product. The accepted mechanism depicted in Scheme 1, includes the oxidative addition of the organic electrophile (generally halides, pseudohalides) to the transition metal followed by transmetalation and reductive elimination reaction.[7]

In 1963, Castro and Stephen discovered the synthesis of diarylacetylenes by the cross-coupling between copper acetylides and aryl halides under refluxing pyridine.[8] Later, Sonagashira observed that the coupling between terminal alkynes with aryl halides occurred in presence of catalytic amount of palladium and copper.[9] Consequently, a number of modifications have been made toward the use of catalytic amount of transition metals in the coupling reactions.

Scheme 1. General mechanism of cross-coupling reactions



Among the TM-based catalyst, Pd-catalysts are extensively used for various coupling reactions. In spite of having wide scope and excellent compatibility with many functional groups, these protocols, often suffer from the disadvantages resulting from (i) the high cost of the palladium precursors, (ii) the need for ancillary ligands rendering the catalysts sufficiently reactive, (iii) concerns about the toxicity of these metal salts, and (iv) the extended reaction times, which are necessary in many cases. Considering the cost and environmental factor, the use of Cu and Fe catalysts for various coupling reactions is attractive one from industrial perspectives.[10] Buchwald and Taillefer independently made remarkable development in this arena by conducting the Cu-mediated cross-coupling reactions in the presence of chelating ligands.[11] Use of ligands in such processes not only accelerates the rate of coupling reaction, but also softens the reaction conditions aiming to wide substrate scope. Although several reports describe the advantages of ligand-assisted copper- and/or iron-catalyzed coupling reactions, but separation and regeneration of catalyst often impede its wide utility. Hence, several heterogeneous catalytic systems have been developed. Our efforts toward the Cu/Fe-based catalytic protocol for the C-C, C-N and C-S bond forming reactions have been presented in this thesis. The present chapter describes the Cu/Fe-catalyzed various C-C, C-N and C-S cross-coupling reactions under homogeneous as well as heterogeneous catalytic systems. Towards the end of this chapter, objectives of the present work are depicted briefly.

1.2. C-C cross-coupling reactions

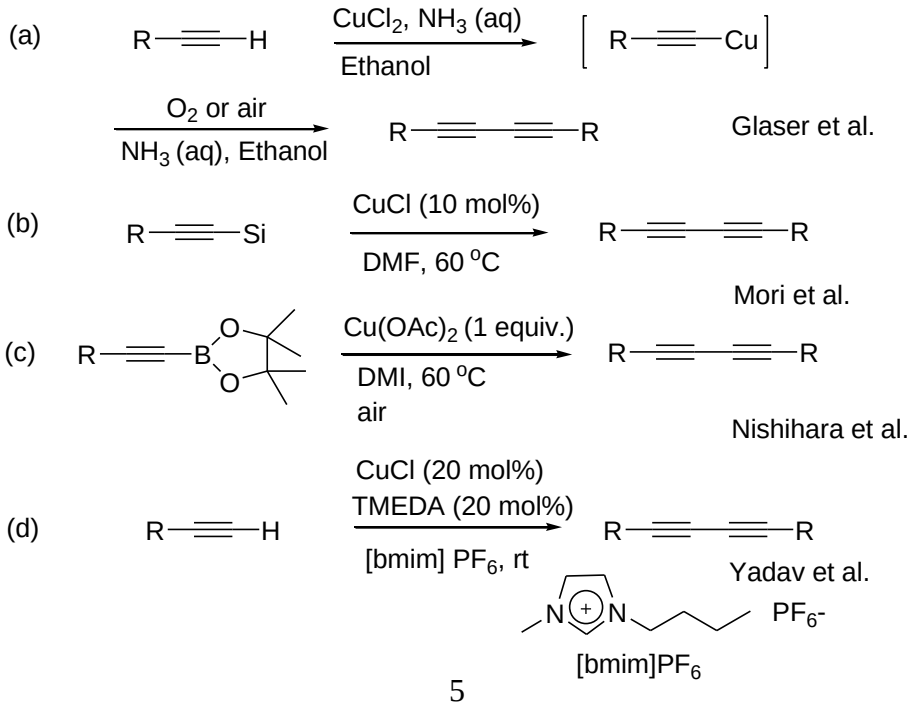
During last five decades, dramatic progress has been made on transition-metal-catalyzed C-C bond forming reactions. Numerous research groups stretch their research objective towards

the development of new catalytic systems with wide substrate scope under mild reaction conditions. As a result of which vast number of methodologies for several types of C-C bonds (viz, C(sp)-C(sp), C(sp2)-C(sp2), C(sp)-C(sp2), C(sp3)-C(sp3), C(sp2)-C(sp3)) forming reactions have been explored.[12] The pioneering work of Miura on copper-catalyzed synthesis of aryl alkynes (C(sp)-C(sp2) coupling) draws the rigorous attention of chemists toward the copper-mediated C-C coupling reactions. Later, Fe-catalyzed C-C coupling reactions were also developed. Here, we briefly describe the systematic progress on Cu/Fe-catalyzed various C-C cross-coupling reactions.

C(sp)-C(sp) bond formations

The copper promoted acetylenic coupling is found its application in the synthesis of natural products as well as functional materials.[13] Glaser, in 1869 first reported the copper-catalyzed dimerization of terminal alkynes to diacetylenes through the C(sp)-C(sp) bond forming reaction. In this reaction, stoichiometric amount of copper salt is needed to form copper acetylene intermediate which subsequently oxidized in presence of air or O_2 to give symmetrical diynes (Scheme 2a).[2] The advantages of this C(sp)-C(sp) bond forming reaction were appreciated by the synthetic community during the following decades by exploring a number of synthetic variations to the Glaser coupling. These variants differ from the original coupling with respect to oxidants, substrates and amount of copper catalyst.

Scheme 2

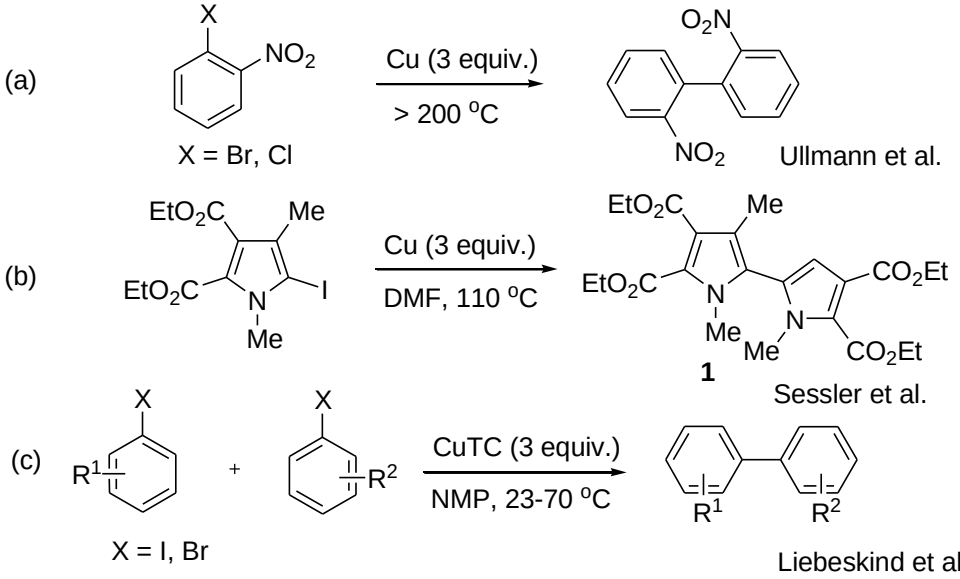


Significantly, Hay dimerized the terminal alkynes at room temperature by using catalytic amount of CuCl in pyridine.[14] Terminally silicon substituted alkynes, such as alkynylsilanes were also employed for Glaser homocoupling reactions by Mori and co-workers using catalytic amount of CuCl in DMF (Scheme 2b).[15] Later, Nishihara reported the similar homocoupling reactions by choosing alkynylboronates as coupling partner in the presence of stoichiometric amount of copper acetate (Scheme 2c).[16] Yadav and co-workers made an improvement by conducting the ligand-assisted copper-catalyzed dimerization of terminal alkynes in presence of ionic liquid (e.g. [bmim]PF_6) (Scheme 2d).[17]

C(sp2)-C(sp2) bond formations

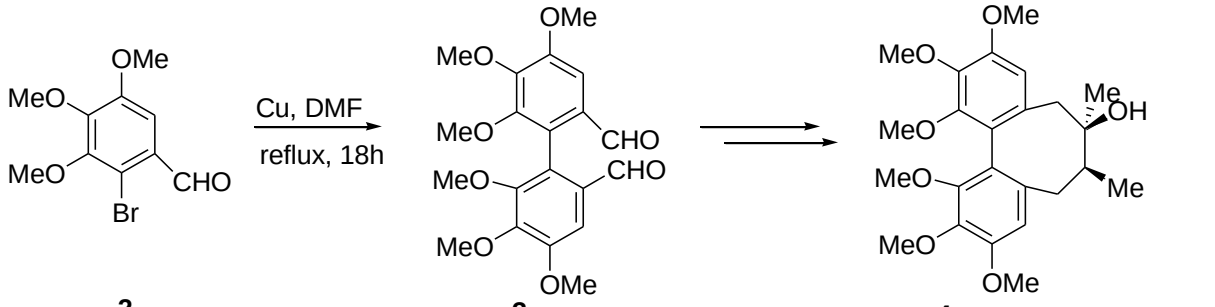
Following the conceptual development on C(sp)-C(sp) homocoupling by Glaser, similar Cu-mediated method was adopted by Ullmann in 1901, for the construction of C(sp2)-C(sp2) bond between aryl halides. He reported the dimerization of 2-bromo- and 2-chloronitrobenzene in presence of superstoichiometric amount of copper sources at high temperature (≈220 °C) (Scheme 3a).[3] In spite of the harsh reaction conditions, Ullmann reaction was followed by the organic community for a long time to achieve biaryls. Since last six decades, numerous efforts have been made to extend the substrate scope as well as to soften the reaction conditions intending to the formation of less amount of waste by converting the coupling process to a catalytic one. A modified methodology includes the use of DMF as solvent permits the coupling reaction to occur at lower temperature.[18]

Scheme 3



Sessler et al. utilized activated Cu(**0**) obtained from the reduction of CuI with potassium, for the synthesis of substituted 2,2'-bipyrroles **1** at relatively lower temperature (110 °C) (Scheme 3b).[19] Further decrease in temperature was observed by Liebeskind and his co-workers by applying copper (**I**)-thiophene-2-carboxylate (CuTC) in NMP (Scheme 3c).[20] The modified Ullmann coupling reactions were found applications in total synthesis of natural and non-natural products. For instance, **3,** an intermediate for (+)-isoschizandrin **4,** was synthesized readily by the copper-catalyzed homocoupling of the corresponding bromide **2** (Scheme 4).[21]

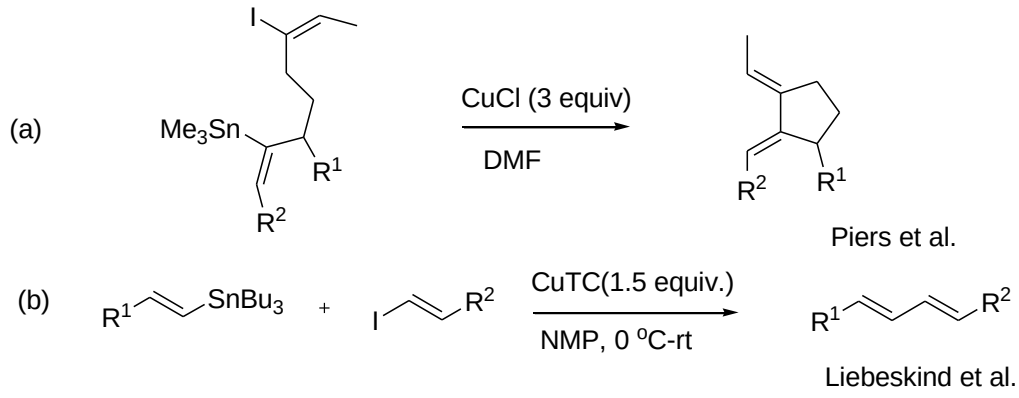
Scheme 4



2 **3** **4** Isoschizandrin

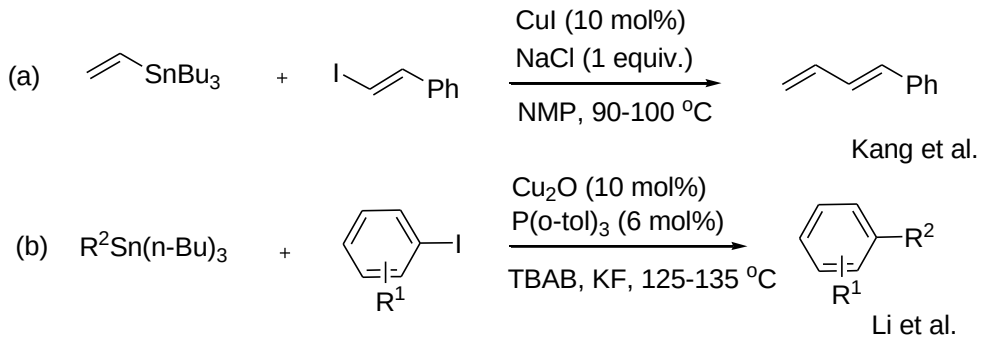
Another method for C(sp2)-C(sp2) bond forming reaction is the coupling between the organic electrophiles with the organotin reagents. Piers and co-workers reported a copper-catalyzed coupling reaction toward the synthesis of conjugated dienes by intramolecular coupling between vinyltrimethyl stannane with vinyl iodide derivatives (Scheme 5a). This reaction might be a Cu-catalyzed analogue of Stille coupling reaction.[22] Further, organostannanes were used for the intermolecular cross-coupling with the aryl, heteroaryl and vinyl iodides to give unsymmetrical 1,3-dienes in the presence of stoichiometric amount of copper(**I**) thiophene carboxylate (CuTC) (Scheme 5b).[23]

Scheme 5



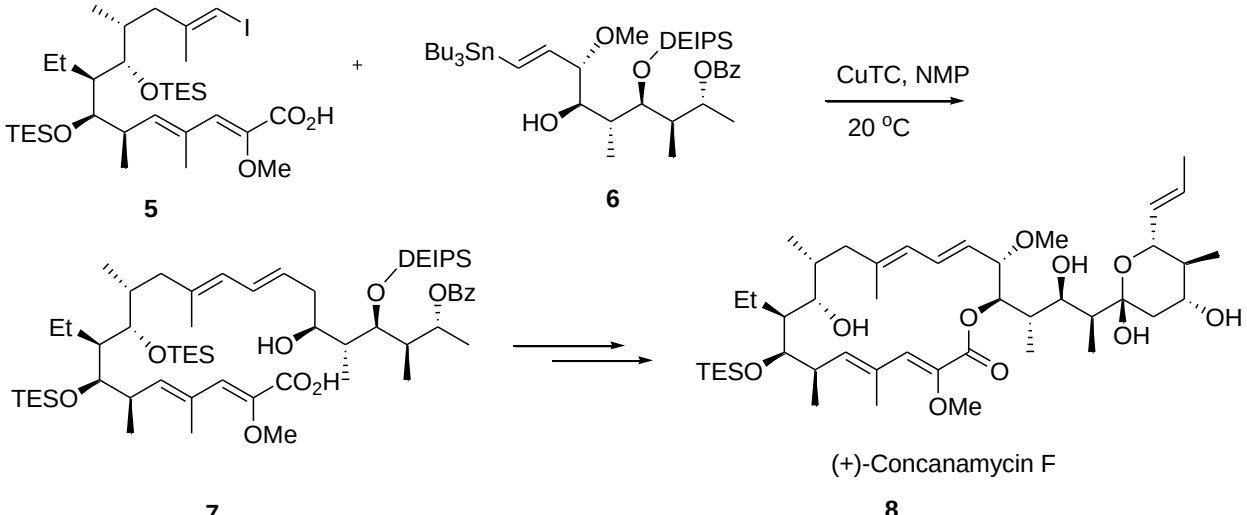
The copper-promoted catalytic version of the above type of coupling reactions was further developed by Kang and co-workers. They described the cross-coupling between organostannanes with aryl iodides using catalytic amount of CuI in NMP (Scheme 6a).[24] However, addition of stoichiometric amount of sodium chloride is essential for the optimum yield. Li et al. developed a ligand-assisted Cu_2O nanoparticles-mediated coupling of organotins with aryl halides in TBAB.[25] With aryl iodides and activated aryl bromides, the later catalytic system was recycled up to five consecutive runs. However, in case of deactivated aryl bromides the efficiency of the catalyst was limited to single run (Scheme 6b).

Scheme 6



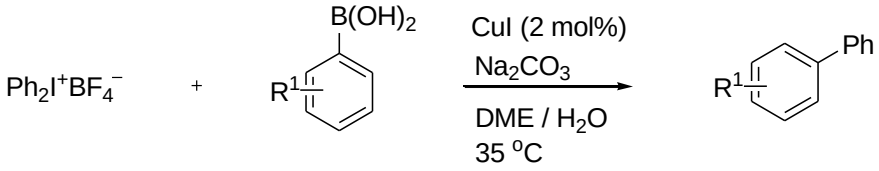
Copper-catalyzed cross-coupling between organotin derivatives with vinyl iodide has been exploited for the total synthesis of complex natural products. For example, Peterson and his co-workers performed the total synthesis of Concanamycin **8** in which the intermediate **7** was prepared by the copper-mediated coupling between vinyl iodide derivatives **5** and vinyl stannane derivatives **6** (Scheme 7).[26]

Scheme 7



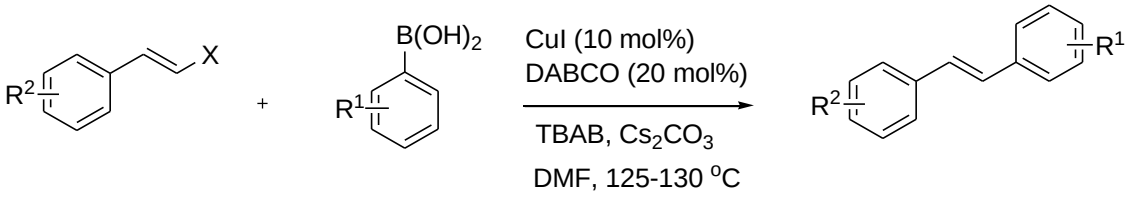
The cross-coupling between arylboronic acids with aryl and vinyl halides has been emerged as potential method for the formation of C(sp2)-C(sp2) bond. This method has several advantages including the use of commercially available starting materials, generation of non-toxic by-products, negligible effect of steric hinderance and good functional group tolerance. In 1996, Kang and co-workers reported the CuI catalyzed coupling between boronic acid derivatives and iodonium salts in aqueous DME to give biaryls (Scheme 8).[27]

Scheme 8



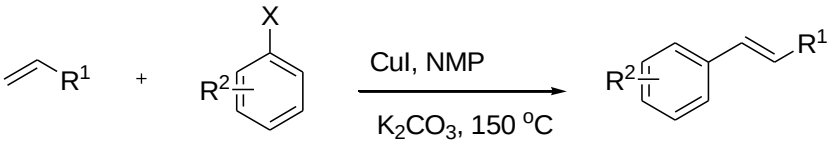
Furthermore, ligand-assisted copper-catalyzed coupling between arylboronic acids with vinyl halides and aryl halides was developed by Li et al. (Scheme 9). They found that in the presence of TBAB and CuI, the coupling reactions proceed smoothly to afford diarylethenes and polyaryls in moderate to good yield.[28]

Scheme 9



The copper-catalyzed C(sp2)-C(sp2) coupling was also possible between the aryl and vinyl halides with the olefins. In 1997, Iyer reported the synthesis of aryl-alkenes and conjugated alkenes by coupling between olefins with aryl and vinyl iodides using stoichiometric amount of copper iodide in N-methylpyrolidone (NMP) (Scheme 10).[29] Use of DABCO as a ligand in such coupling reaction was also reported.[30]

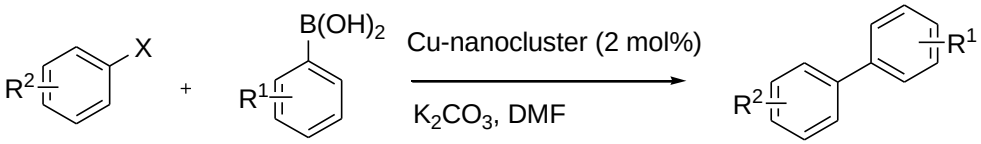
Scheme 10



In spite of significant developments on copper-based homogeneous catalytic systems for C(sp2)-C(sp2) coupling reactions, the use of heterogeneous catalytic system also daunting. Mao et al. applied the readily available copper powder for the coupling between aryl iodides with boronic

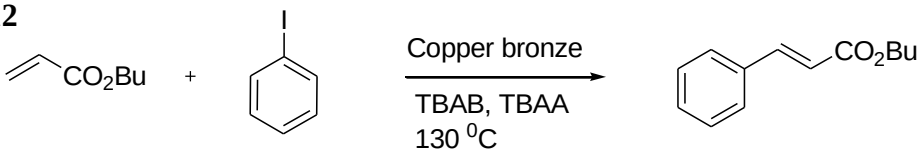
acids in PEG-400. Using iodine as additive, the coupling between aryl bromides and chlorides with boronic acids was found to be successful.[31] Rothenberg and co-workers applied the copper nanocluster for the coupling between aryl halides and arylboronic acids (Scheme 11). Di- and trimetallic clusters showed enhanced reactivity in the coupling of arylboronic acids with activated aryl bromides and aryl chlorides.[32]

Scheme 11



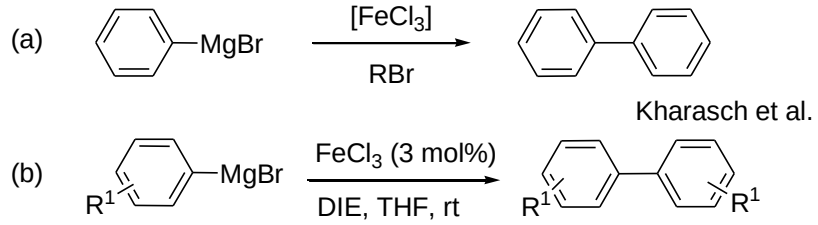
Copper nanoparticles were also employed to achieve the bond between aryl iodides and butyl acrylates. The copper nanoparticles were formed in-situ by reduction of copper bronze with aryl iodides in TBAB and TBAA (Scheme 12).[33]

Scheme 12



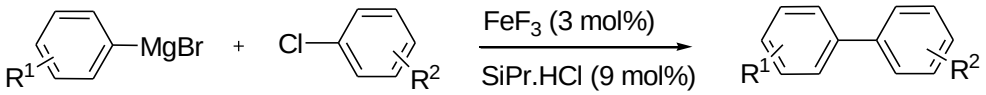
Iron catalysts were also employed for C(sp2)-C(sp2) bond forming reactions. In 1941, Kharasch and Field first reported the iron-catalyzed homocoupling of Grignard reagent for the synthesis of symmetrical biaryls (Scheme 13a).[34] Later, the homocoupling of Grignard reagent was extended to include a wide range of substrate for the synthesis of biaryls (Scheme 13b).[35]

Scheme 13



Unsymmetrical biaryls were synthesized by iron-mediated cross-coupling between aryl magnesium bromides and aryl chlorides as described by Nakamura and his co-workers (Scheme 14).[36]

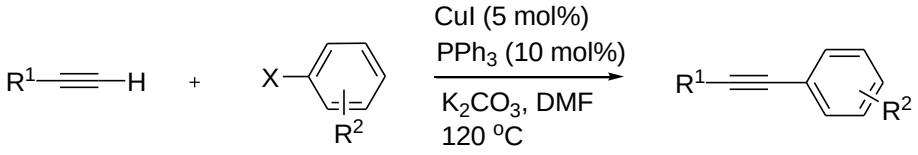
Scheme 14



C(sp)-C(sp2) bond formations

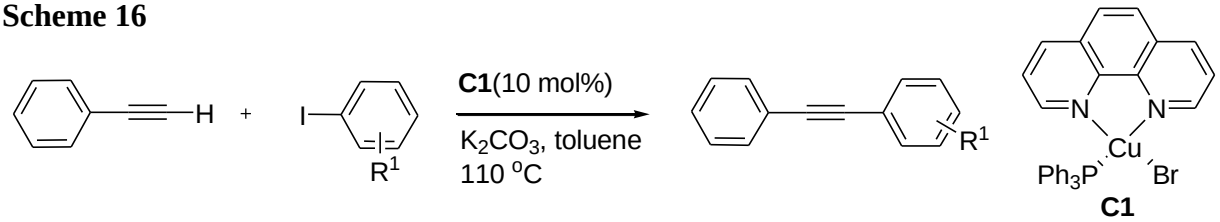
The coupling between alkynes with aryl and vinyl halides resulted the formation of C(sp)-C(sp2) bond**.** In 1993, Miura and co-workers reported ligand-assisted copper-catalyzed synthesis of aryl-alkynes and vinyl-alkynes by coupling terminal alkynes with aryl halides and vinyl halides respectively (Scheme 15).[37] Under a similar catalytic condition, Li and his co-workers prepared the aryl-alkynes in the presence of DABCO as a chelating ligand.[38]

Scheme 15



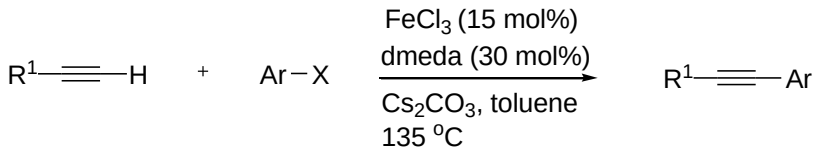
Later, Venkataraman et al. observed that if the solubility of the copper salts were increased, the reaction would occur at mild conditions. They prepared a soluble copper complex (**C1**) and conducted the C(sp)-C(sp2) coupling between phenylacetylenes and aryl iodides in toluene. (Scheme 16).[39]

Scheme 16



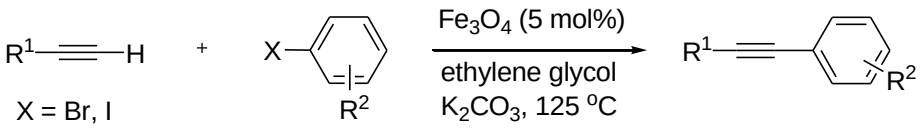
Although copper-catalyzed sp-sp2 coupling reactions were well reported the development of iron-catalyzed C-C coupling reactions were also encouraging because of cheap and environmental friendly nature of iron. Bolm and co-workers developed an iron-catalyzed elegant methodology for the formation of C(sp)-C(sp2) bond. They found that $FeCl_3$ in combination with DMEDA leads to the coupling between terminal alkynes with aryl halides in refluxing toluene (Scheme 17).[40]

Scheme 17



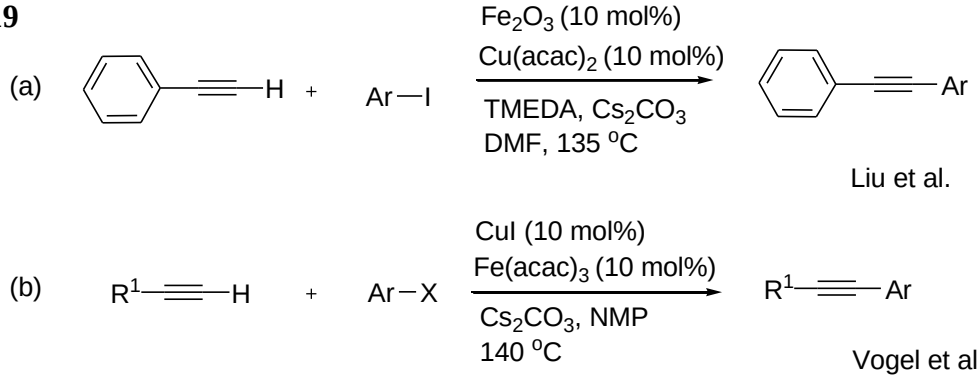
Recently heterogeneous, recyclable Fe_3O_4 nanoparticles-mediated coupling between terminal alkynes with aryl and heteroaryl halides in ethylene glycol were reported by Firouzabadi et al. (Scheme 18).[41]

Scheme 18



Although the Cu/Fe-catalyzed C(sp)-C(sp2) cross-coupling reactions were encouraging, there is considerable scope for further improvement. For instance, Bolm's iron-mediated coupling reactions required long reaction time (72 h), and the reaction of aliphatic alkynes was less successful. Furthermore, the Cu and Fe-mediated methodologies suffer from a relatively narrow substrate scope. Evidently, the coupling between heterocyclic alkynes with aryl halides or heterocyclic halides has not been reported. Hence, development of mild and efficient catalytic system toward the sp-sp2 coupling reactions was encouraging. In this respect, use of cheap and environmental benign iron salts in combination with copper is noteworthy. Liu et al. described a ligand-assisted Cu-Fe co-catalytic method for the C(sp)-C(sp2) coupling reactions. They found that Fe_2O_3 in combination with $Cu(acac)_2$ was suitable for the cross-coupling between terminal alkynes with aryl and heteroaryl halides using TMEDA as the ligand (Scheme 19a).[42] Later, Vogel and his co-workers reported CuI/$Fe(acac)_3$ catalytic system for the synthesis of aryl-alkynes (Scheme 19b).[43]

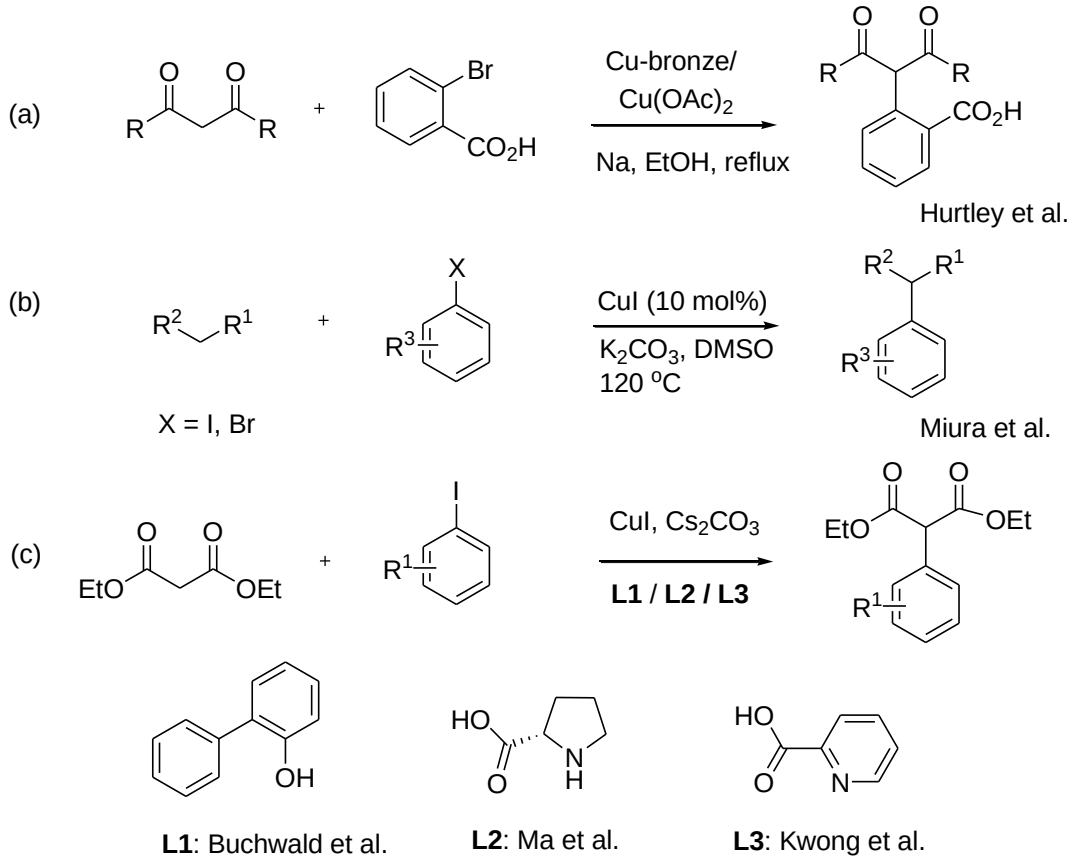
Scheme 19



C(sp2)-C(sp3) bond formations

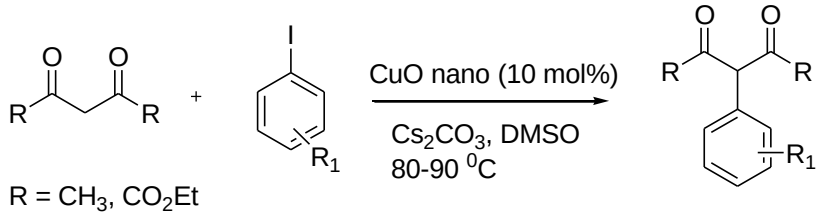
In 1929, Hurtley observed that sodium salt of diketones or malonates could be arylated by the reaction of 2-bromobenzoic acid in presence of catalytic amount of copper-bronze or copper acetate (Scheme 20a, Hurtley reaction).[44] Usually, this reaction, requires ortho-directing group as well as a strong base. Extensive efforts were then made to develop mild reaction conditions. Miura et al. in 1993, reported a copper-mediated sp2-sp3 coupling between active methylene compounds with aryl iodides in DMSO (Scheme 20b).[45] Later, ligand-assisted copper-promoted coupling reactions were developed which proceed at lower temperature (Scheme 20c). Evidently, Buchwald and his co-workers observed that addition of ligands like 2-phenylphenol **L1** reduce the reaction temperature.[46] Subsequently, ligands such as L-proline **L2**[47] and 2-picolinic acid **L3**[48] were employed for the coupling between 1,3-diketones with aryl iodides and bromides.

Scheme 20



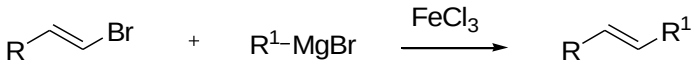
Heterogeneous copper nanoparticles were also employed for C(sp2)-C(sp3) coupling reactions. For instance, Kidwai and co-workers reported the recyclable CuO nanoparticle-mediated coupling between 1,3-diketones with aryl iodides in DMSO (Scheme 21).[49]

Scheme 21



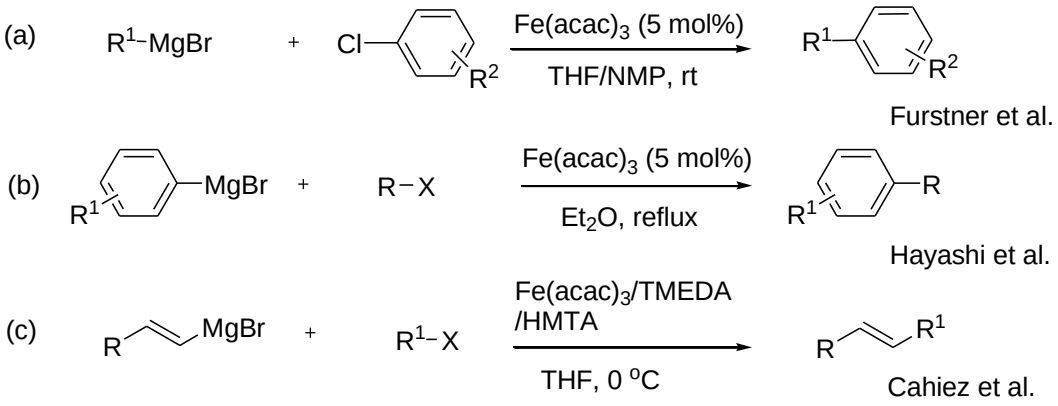
Besides, iron-catalyzed such coupling reactions were also well reported. Evidently, in 1971, Kochi first exploited the iron catalyst (e.g. $FeCl_3$) for the cross-coupling between alkyl Grignard reagents with alkynyl bromides (Scheme 22).[50]

Scheme 22



Later, Früstner and Leitner employed $Fe(acac)_3$ for the cross-coupling between activated aryl chlorides and alkyl Grignard reagents in a mixture THF and NMP (Scheme 23a).[51] Furthermore, the above catalytic system was applied for coupling between aryl Grignard reagents with primary and secondary alkyl halides in refluxing diethylether (Scheme 23b).[52] A mild protocol for the stereoselective sp2-sp3 couplings were demonstrated by Cahiez and his co-workers. They used similar catalyst in presence of chelating ligands, like TMEDA and HMTA for the coupling of vinyl Grignard with alkyl halides (Scheme 23c).[53]

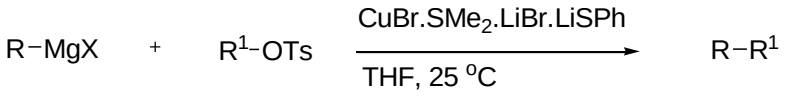
Scheme 23



C(sp3)-C(sp3) bond formations

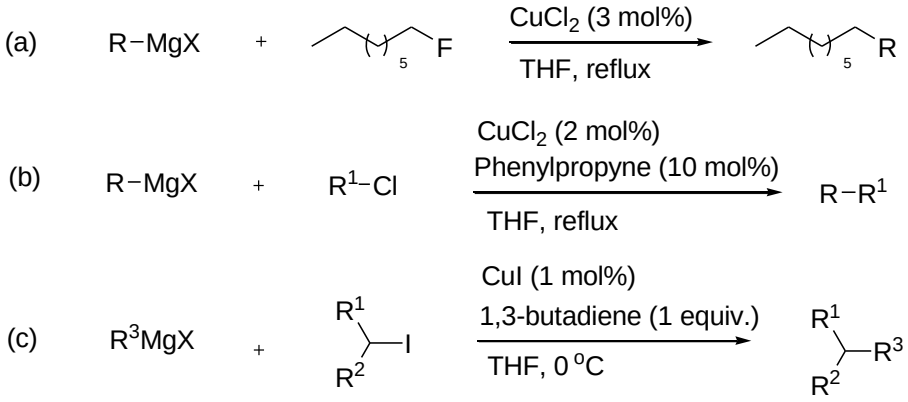
The C(sp3)-C(sp3) coupling reactions between alkyl derivatives were less reported as compared to other types of C-C coupling reactions discussed earlier. This is may be due to the alkylmetal intermediate generated in situ in the catalytic cycle undergoes *β*-hydride elimination reaction. Moreover, this intermediate also participates in other undesired reactions.[54] In 1997, Burns and his co-workers reported a copper-catalyzed sp3-sp3 coupling reaction between alkyl Grignard reagents with alkyl pseudohalides (Scheme 24).[55]

Scheme 24



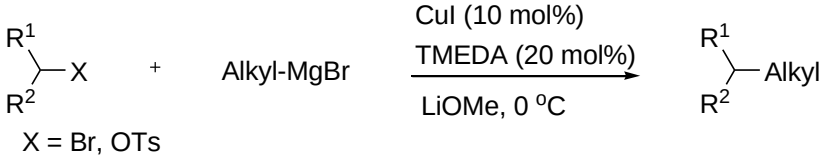
Later, Kambe et al. developed the CuCl catalyzed coupling between octyl fluorides and alkyl Grignard reagents (Scheme 25a).[56] The same group further also used 1-phenylpropyne[57] and 1,3-butadiene[58] separately as additives to broaden the substrate scope of the sp3-sp3 bond forming reaction (Scheme 25b, Scheme 25c).

Scheme 25



Recently, copper-mediated C(sp3)-C(sp3) cross-coupling between non-activated secondary alkyl halides and pseudohalides with secondary Grignard reagents were reported by Liu et al.[59] The C-C bond formations were possible by using CuI as catalyst and TMEDA as additive (Scheme 26).

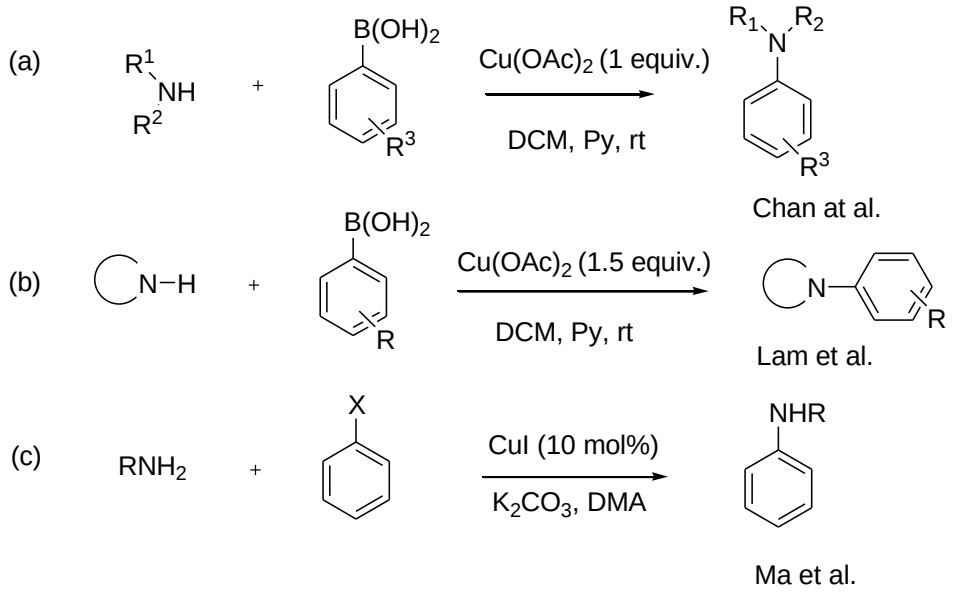
Scheme 26



1.3. C-N cross-coupling reactions

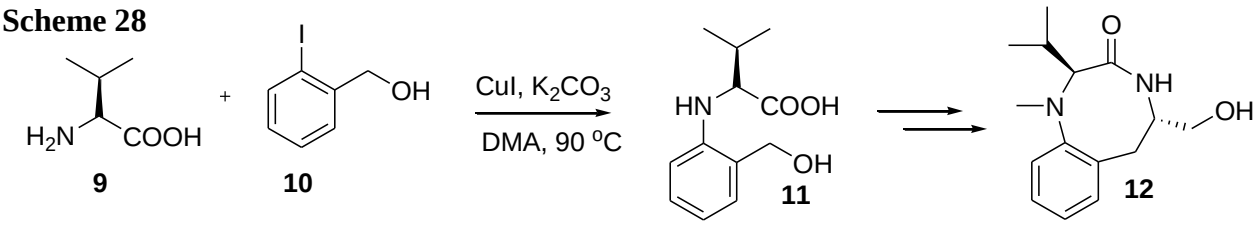
Transition-metal-mediated C-N cross-coupling reactions constitute a powerful strategy for the synthesis of numerous compounds of biological importance.[60] Since 1903, Ullmann cross-coupling is used traditionally for the C-N bond forming reactions.[4] However, requirement of stoichiometric amounts of copper reagent and high temperature impede the industrial application of such reaction. In order to circumvent the above limitations considerable developments have been made focusing cheap, eco-friendly catalytic systems and mild reaction conditions. In this regard, we wish to present the significant developments on Cu/Fe-catalyzed C-N cross-coupling reactions.[10] Notably, after 95 years of Ullmann C-N cross-coupling reaction, Chan,[61] Lam[62] and Ma[63] made a breakthrough independently by softening the Ullmann reaction conditions i.e., by reducing the reaction temperature from 200 °C to room temperature in presence of stoichiometric amount of copper acetate (Scheme 27).

Scheme 27



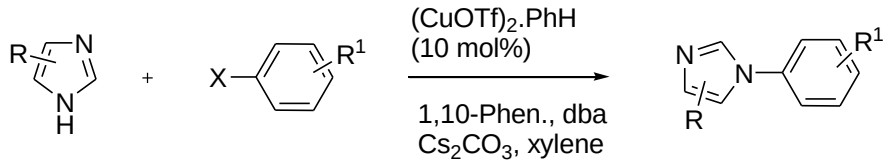
Ma et al. also applied their methodology towards the synthesis of Benzolactam V8, **12** in which the intermediate **11** was formed by the cross-coupling between **9** and **10** (Scheme 28).[63]

Scheme 28



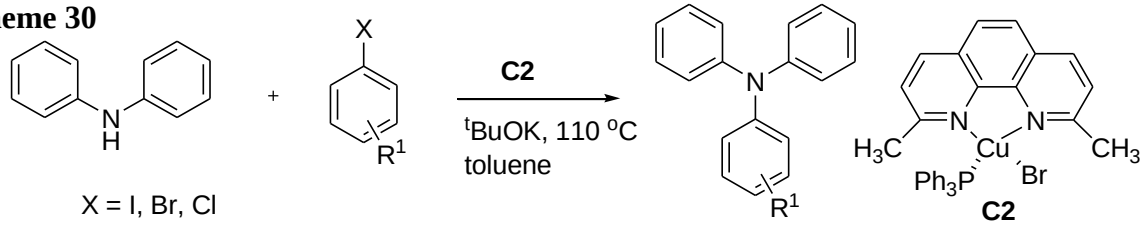
Later, Buchwald et al. initiated ligand-assisted Cu-catalyzed C-N cross-coupling reaction. They N-arylated the imidazoles with aryl halides in presence of catalytic amount of $(CuOTf)_2$ and stoichiometric amount of 1,10-phen.(Scheme 29).[64]

Scheme 29



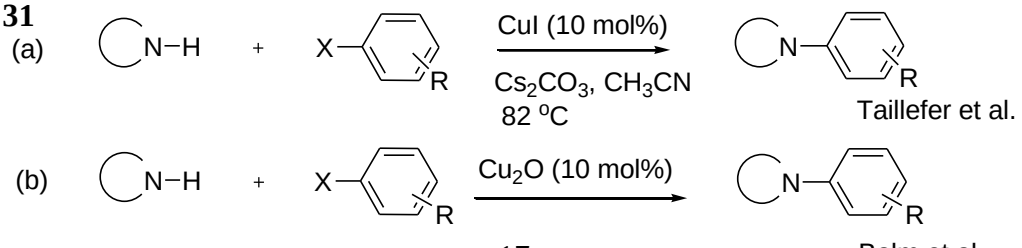
Venkataraman and co-workers prepared a soluble copper catalyst (**C2)** and applied for the C(aryl)-N cross-coupling reaction between diarylamines with aryl halides in refluxing toluene (Scheme 30).[39]

Scheme 30



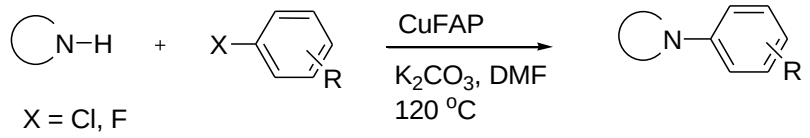
Subsequently, numerous N, O-containing ligands such as L-proline, N-methylglycine, N,N'-dimethylcyclohaxane-1,2-diamine, DPP, 1,3-diketone, 4,7-dimethoxy-1,10-phen., 8 hydroxyquinoline, 2-aminopyrimidine-4,6-diol, *rac*-BINOL, 4,7-dimethoxy-1,10-phenanthroline, ninhydrin etc. were employed for the copper-mediated C-N coupling reactions.[10] On the other hand, the simple separation and regeneration of the catalyst from the reaction mixture are in strong demand for the cost-effective process of molecular synthesis. Thus, ligand-free cross-coupling reactions were evolved. The earliest contributions were made by Taillefer and co-workers. They performed the coupling between iodo- and bromobenzene with nitrogen heterocycles using catalytic quantity of CuI in CH_3CN (Scheme 31a).[65] Later, Bolm et al. proposed Cu_2O-mediated C-N coupling between azoles with aryl iodides and bromides in DMF under ligand-free conditions (Scheme 31b).[66]

Scheme 31



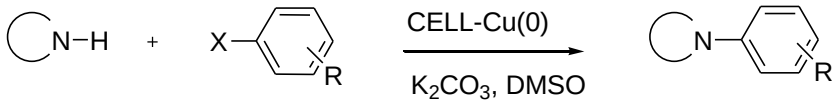
Numerous heterogeneous catalysts were developed for the C-N cross-coupling reactions aiming at the simple purification and reusability of the catalyst. One interesting example was reported by Choudary and his co-workers, in which the supported copper fluoroapatite (CuFAP) was used for N-arylation of numerous N-containing heterocycles even with unreactive aryl chlorides and aryl fluorides (Scheme 32).[67]

Scheme 32



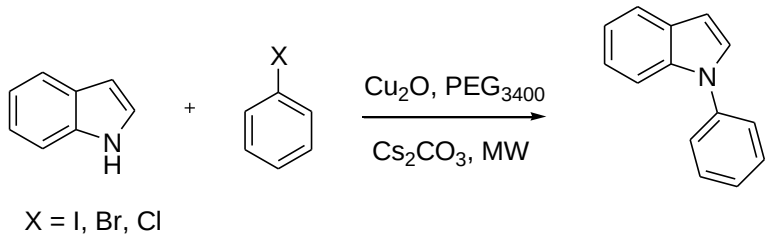
Kantam and her co-workers demonstrated a ligand-free, reusable cellulose-supported Cu(**0**)-catalyzed N-arylation of NH-heterocycles with aryl bromides and iodides in DMSO (Scheme 33).[68]

Scheme 33



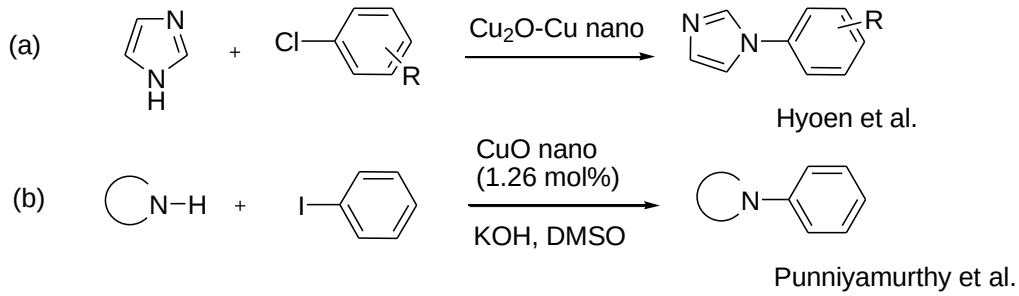
Copper(**I**) oxide in PEG support were also developed as a recyclable catalyst for the C-N cross-coupling reactions. Lamaty et al. reported microwave assisted Cu_2O-PEG for the coupling between benzimidazoles and indoles with aryl halides (Scheme 34).[69]

Scheme 34



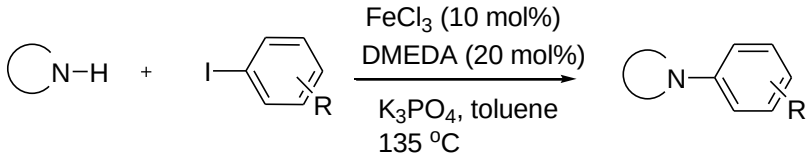
The reusable copper nanoparticles were also utilized for the C-N cross-coupling reactions exploiting the high surface area and low coordination sites of the catalyst. Evidently, Hyeon and co-workers used Cu_2O-coated Cu nanoparticles for the coupling between nitrogen nucleophiles with activated aryl chlorides (Scheme 35a).[70] Later, CuO nanoparticles were successfully employed by Punniyamurthy et al. for the N-arylation of various N-containing precursors (Scheme 35b).[71]

Scheme 35



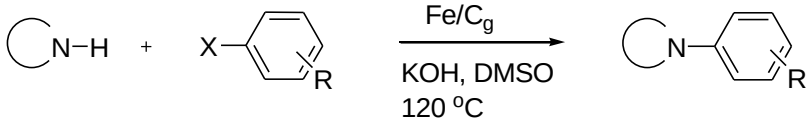
In addition to the significant progress on Cu-catalyzed C-N cross-coupling reactions, the Fe-catalyzed reactions are also emerged. The pioneering efforts on Fe-catalyzed C-N coupling reactions were made by the Bolm. They showed the potential of $FeCl_3$ in presence of DMEDA for the N-arylation of NH-heterocycles with differently substituted aryl iodides and bromides in refluxing toluene (Scheme 36).[72]

Scheme 36



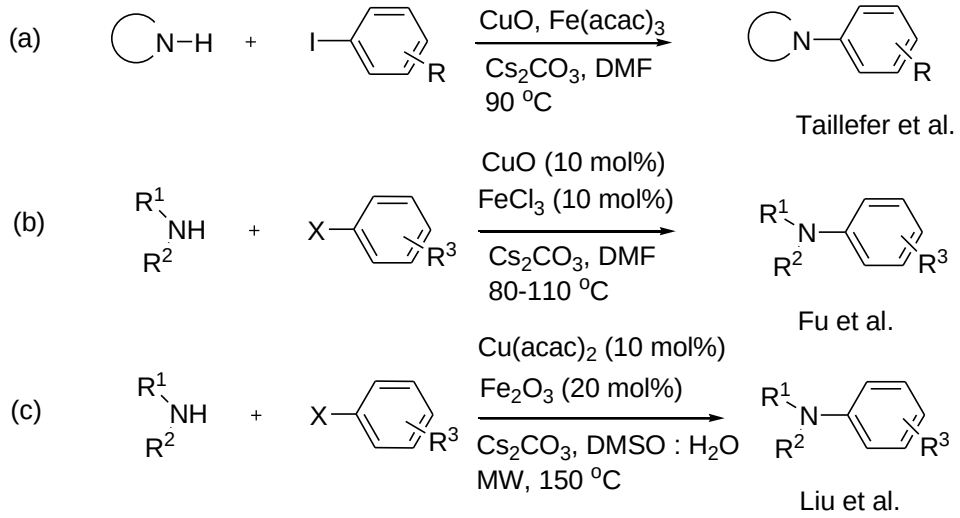
Later, Rama Rao prepared recyclable graphite supported iron catalyst and applied for the coupling between nitrogen heterocycles with aryl halides under ligand-free conditions (Scheme 37).[73]

Scheme 37



The Cu-Fe co-operative catalysts were also developed for the C-N cross-coupling reactions to extend the scope as well as to improve the yield. In 2006, Taillefer and co-workers illustrated the first example on copper/iron co-catalyzed protocol for the N-arylation reaction of various nitrogen heterocycles with aryl halides including the less reactive activated aryl chlorides in DMF (Scheme 38a).[74]

Scheme 38

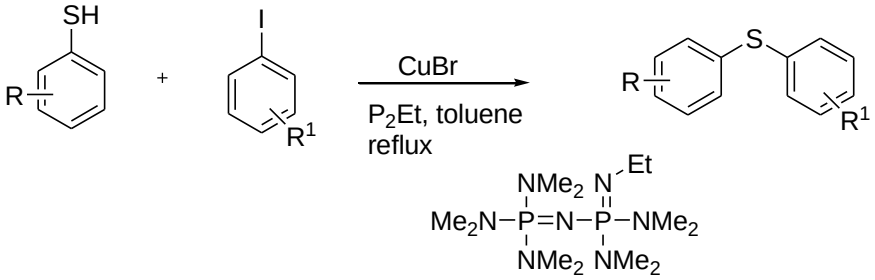


Fu and co-workers employed a mixture of $FeCl_3$ and CuO in presence of *rac*-BINOL to promote the N-arylation reactions (Scheme 38b).[75] Later, the group of Liu reported microwave assisted ligand-free $Cu(acac)_2$-Fe_2O_3 mediated C-N coupling reactions in aqueous DMSO (Scheme 38c).[76] The bimetallic Cu-Fe catalyst represents the economically competitive alternative to the usual copper-ligand combination.

1.4. C-S cross-coupling reactions

Aryl sulfides have significant relevance from clinical interests and biological, pharmaceutical aspects.[77] The transition-metal-catalyzed carbon-sulfur bond forming reaction represents an important tool for the practical synthesis of sulfides.[78] Evidently, among the TM-catalyzed coupling reactions, C-S cross-coupling received less attentions in comparison to C-N and C-O cross-coupling reactions, because: (i) thiols are prone to undergo oxidative S-S coupling reactions to undesired disulfides and (ii) strong coordinating properties of organic sulfur compounds, often make the catalyst ineffective (catalyst poison). Many transition metals such as Pd, Ni etc. have been used for the C-S bond forming reactions.[79] However, the cost and toxicity of the above metals limit their large scale applications particularly in pharmaceutical industry. Thus, cheap and less toxic Cu/Fe-based catalysts have been developed for the C-S cross-coupling reactions. In this context, in 2000, Palomo and co-workers reported the copper-mediated C-S coupling reactions for the first time, though similar Pd-catalyzed reaction was reported earlier by Migita. The former group disclosed the S-arylation of thiols with aryl halides in presence of CuBr and Schwesinger's phosphazene base (P_2Et) (Scheme 39).[80]

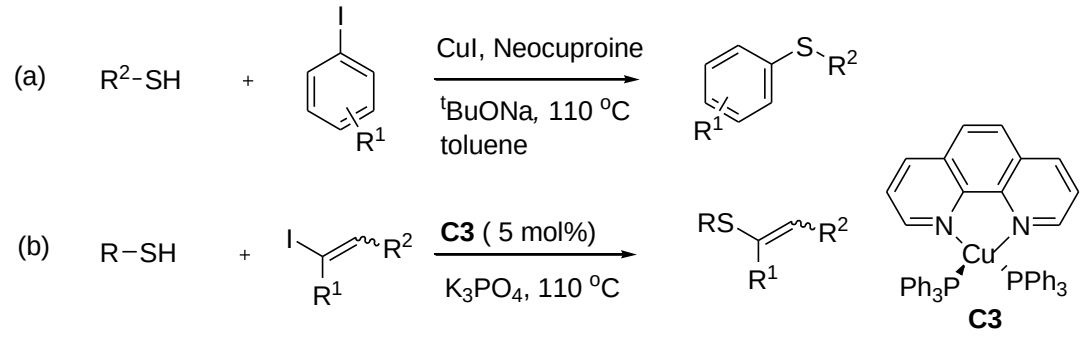
Scheme 39



Schwesinger's phosphazene base

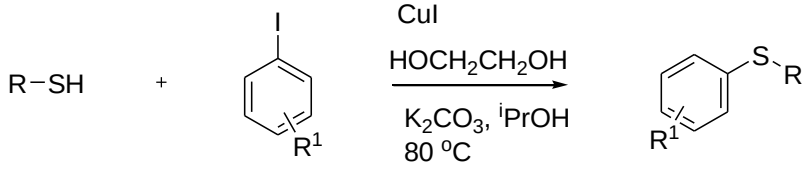
Then after, numerous ligands were used by several groups along with copper salt to expand the scope of C-S cross-coupling reactions. Evidently, Venkataraman and co-workers utilized bidentate ligands such as neocuproine[81] and 1,10-phenanthroline[82] along with copper salt for the cross-coupling of thiols with aryl halides and vinyl halides, respectively, in refluxing toluene (Scheme 40).

Scheme 40



Buchwald et al. S-arylated the thiol derivatives at lower temperature (80 °C) using excess of ethylene glycol as chelating ligand in isopropanol (Scheme 41).[83]

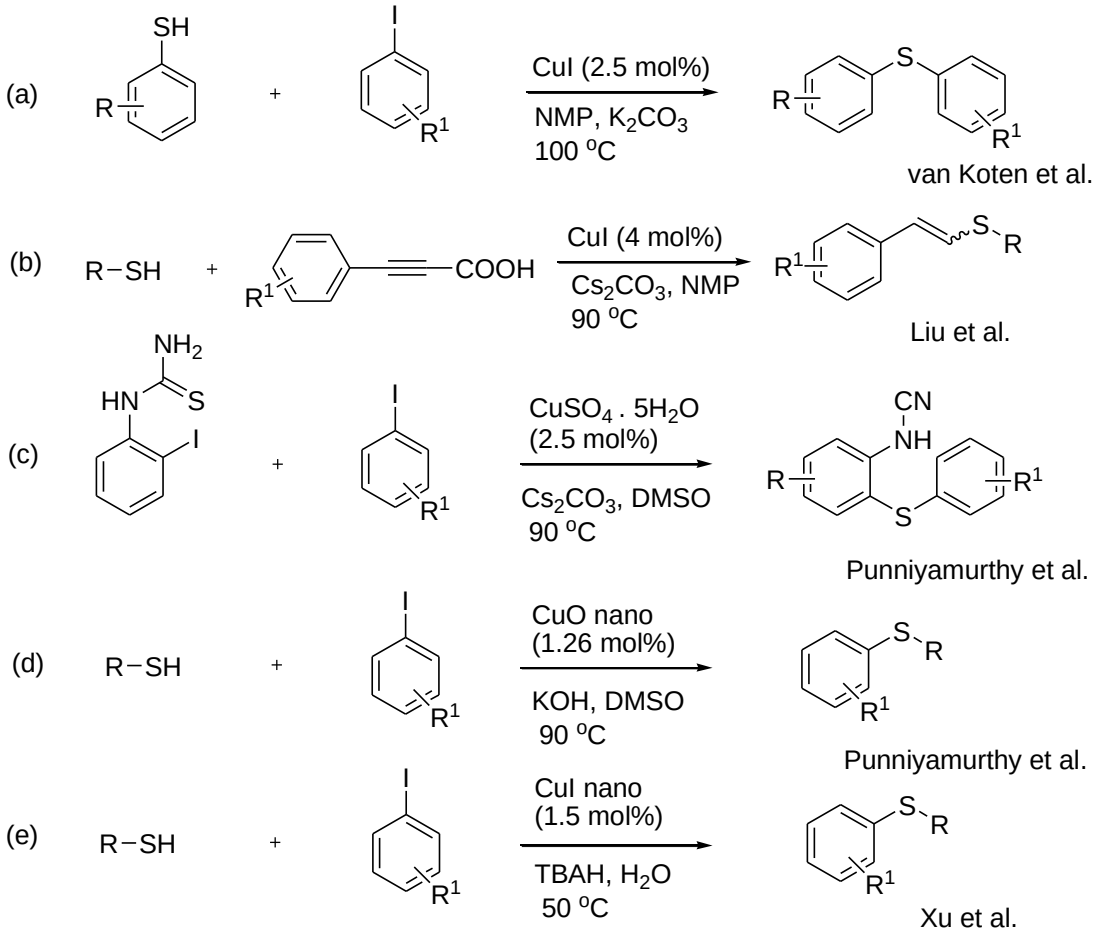
Scheme 41



Subsequently, a number of ligands such as N-methylglycine, oxime-phosphine oxide ligand, tripod ligand, benztriazole, 1,2-diaminocyclohexane, β-ketoester, L-proline, BINAM, 1,2-diols, and ethylene diammine have been exploited by several groups as chelating agents in the copper-catalyzed C-S cross-coupling reactions.[84]

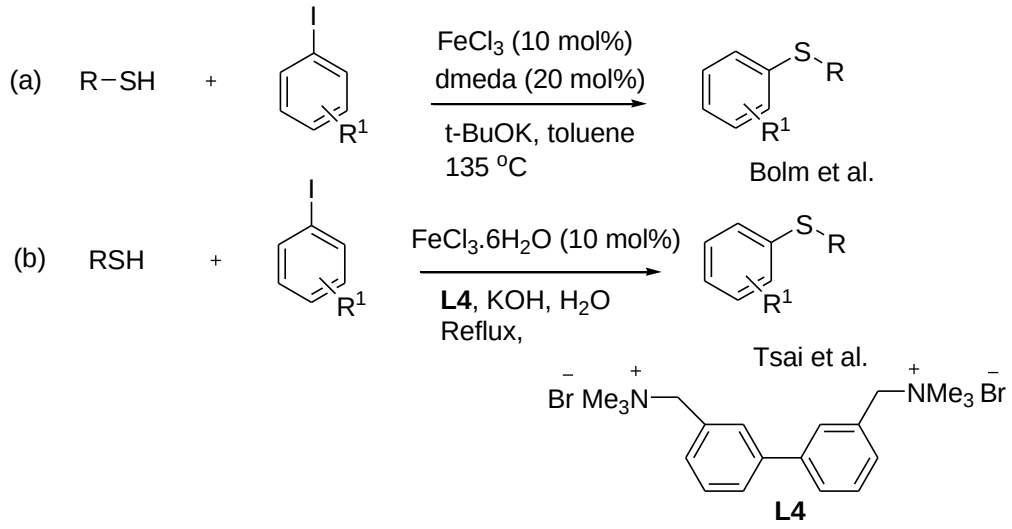
Despite the significant progress in ligand-assisted copper-catalyzed S-arylation reactions, ligand-free reactions are also developed owing to the advantages over purification problem caused by the ligands. For instance, van Koten illustrated the C-S cross-coupling of aryl halides with thiols in the presence of CuI in NMP at 100 °C (Scheme 42a).[85] CuI also catalyzed similar reaction in the presence of PEG at 110 °C.[86] Vinyl sulfides were also prepared by Liu from the decarboxylative C-S cross-coupling between arylpropiolic acids with thiols (Scheme 42b).[87] Punniyamurthy reported a ligand-free copper-promoted S-arylation reaction for the synthesis of 2-(arylthio)arylcyanamides by coupling between 2-(iodoaryl)thioureas with aryl iodides in DMSO (Scheme 42c). Same group was also used CuO nanoparticles for the C-S cross-coupling between thiols with aryl iodides in DMSO at 90 °C (Scheme 42d).[88] Later CuI nanoparticles were utilized for the S-arylation reactions in water by Xu, Feng and co-workers (Scheme 42e).[89]

Scheme 42



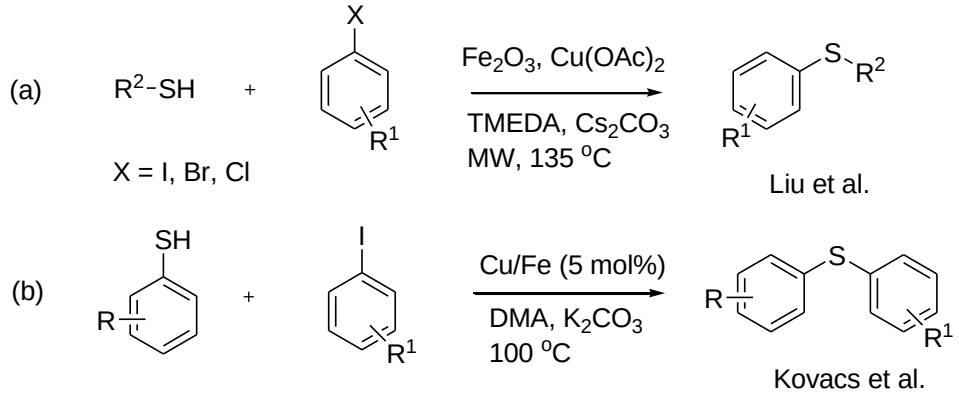
Besides, Cu-based catalytic protocols, iron salts were found useful for the C-S cross-coupling reactions. The most significant advances in this direction were made by Bolm and his co-workers. They found that the combination of $FeCl_3$ and DMEDA was effective for coupling between numerous thiols with aryl iodides (Scheme 43a).[90] Tsai and co-workers were also utilized ligand **L4** to carry out the coupling reactions in aqueous medium (Scheme 43b).[91]

Scheme 43



The synergistic effects of the Cu and Fe on C-S cross-coupling reactions were investigated considering the fact that, iron has the ability to suppress the disulfide formations. Liu et al. disclosed ligand-assisted $Cu(OAc)_2$-Fe_2O_3 co-catalytic system for coupling the thiol derivatives with aryl and heteroaryl halides under microwave irradiations (Scheme 44a).[92] Recently, Kovacs and Novak developed copper on iron heterogeneous catalyst for the S-arylation thiols with aryl iodides (Scheme 44b).[93]

Scheme 44



1.5. Objective of the present work

Cu/Fe-based catalytic systems have shown their potential for various cross-coupling reactions. Besides, the synergistic effects of copper and iron often found to be more promising in cross-coupling reactions. Ligand-assisted Cu/Fe-catalytic systems have been emerged to expand the substrate scope as well as to soften the reaction conditions that are the traditional limitations of coupling reactions. Furthermore, to circumvent the problems associated with the product purification, a number of efficient heterogeneous catalytic systems have been evolved. In spite of tremendous progress in this arena, some of the challenges are remain unsolved. Our objectives in this line are as follows:

1. In most of the coupling reactions, more reactive aryl iodides and aryl bromides are employed as one of the coupling partner, where as the use of less reactive aryl chlorides or sulfonates are limited. Thus, development of new efficient catalytic system that can use less reactive partner for coupling reactions.
2. Development of simple and inexpensive catalyst which works under environmentally benign conditions i.e., green solvents as well as ligand-free or solvent-free conditions is felt necessary.
3. Development of proficient reusable heterogeneous catalytic system for the easy and quantitative separation of the catalyst from the reaction mixture.
4. Considering the potential of Cu/Fe bimetallic co-catalytic systems in cross-coupling reactions, more systematic investigation is required to further exploit the scope of the protocol.

Our efforts in this line to form C-C, C-N and C-S bonds are demonstrated in subsequent chapters. Application of C-C and C-N bond formation strategy for the synthesis of pyrazoles in the presence of cheap and environmental benign Fe-catalyst under solvent free conditions is also presented in the last chapter.

1.6. References

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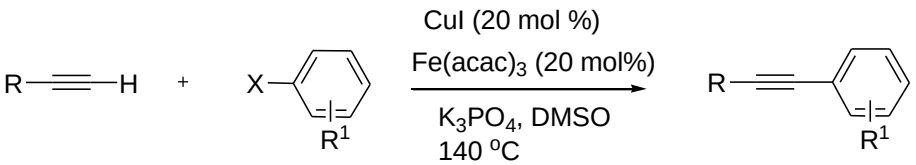
Chapter 2

Cu/Fe-co-catalyzed cross-coupling of terminal alkynes with aryl halides

2.1. Introduction

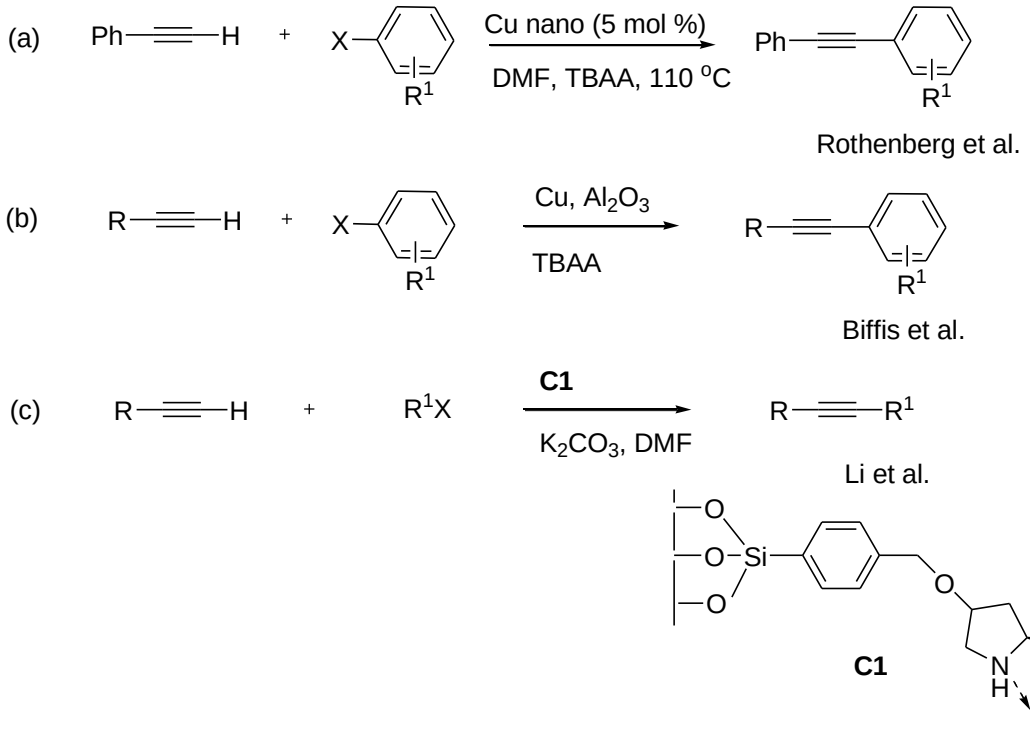
Transition-metal-catalyzed cross-coupling of terminal alkynes with aryl halides has emerged as a robust method in organic synthesis to achieve numerous natural and non-natural products of biological significance.[1] Although the activation of terminal alkyne C-H bond by a quantitative amount of copper iodide was reported earlier by Stephens and Castro,[2] the catalytic version was popularized as the Sonagashira coupling.[3] The latter reaction has been routinely performed using a palladium-based catalyst (e.g., $[Pd(PPh_3)_4]$) and a copper(**I**) salt as co-catalyst to access aryl-alkynes via C(sp)-C(sp2) bond forming reaction. Undoubtedly, this method is having wide scope and excellent compatibility with many functional groups. However, these protocols, often suffer from the disadvantages resulting from (i) the high cost of the palladium precursors (ii) the need for ancillary ligands rendering the catalysts sufficiently reactive (iii) concerns about the toxicity of these metal salts and (iv) the extended reaction times, which are necessary in many cases.[4] Thus, considering the cost and environmental factor, researchers have turned their attention toward the use of less expensive, less toxic, and more efficient metals to replace Pd. Indeed, ligand-assisted copper-catalyzed cross-coupling reactions of alkynes with aryl halides have attracted significant attention due to the low cost and relatively lower toxicity. Various ligands including diamines, amino acids, β-ketoesters, 1,10-phenanthroline derivatives, poly(ethylene glycol), ninhydrin, and other nitrogen- and/or oxygen-containing ligands which chelate copper, have been used for cross-coupling reactions.[5-12] Recently, copper/iron co-catalytic systems were also successfully used for the cross-coupling reactions under homogeneous conditions considering the cheap and environment-friendly behaviour of iron.[13] For instance, Taillefer and co-worker reported the Cu/Fe-co-catalytic method for the coupling between phenylacetylenes with iodobenzene.[13a] Later, Mao et al. illustrated the use of CuI-$Fe(acac)_3$ for the arylation of terminal alkynes. They observed that addition of $Fe(acac)_3$ to CuI significantly improved the cross-coupling product because of the possible suppression of the homocoupling product (Scheme 1).[14]

Scheme 1



In contrast, development of heterogeneous Cu-based catalytic system for C(sp)-C(sp2) cross-coupling reactions has received less attention. For the first time, Rothenberg et al. employed heterogeneous, reusable Cu-nanoclusters for the cross-coupling between alkynes with aryl halides (Scheme 2a).[15]

Scheme 2



Subsequently, Biffis demonstrated the catalytic activity of CuO and Cu on alumina support towards the C(sp)-C(sp2) coupling reactions, but the high degree of copper leaching restricts its reusability (Scheme 2b).[16] Silica-anchored proline-copper(1) **(C1)** have also used as an efficient and reusable catalyst for the coupling of terminal alkynes with aryl halides (Scheme 2c). On recycling, the catalytic activity did not alter even up to six cycles.[17]

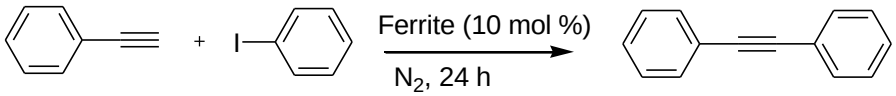
Considering the potential of Cu/Fe-based heterogeneous catalytic systems in cross-coupling reactions, we are interested for the development of a cheap, environmental friendly and reusable heterogeneous catalytic protocol for efficient C(sp)-C(sp2) bond forming reactions. In recent years, due to large surface area and reactive morphology, nanoparticles were exploited widely for their attractive catalytic activity in various reactions.[18] However, the small size of nanoparticles often makes their separation and recycling difficult, which impedes their use in

large scale.[19] In order to circumvent such problems, we thought about the use of superparamagnetic nanoparticles, whose flocculation and dispersion can be controlled reversibly by application of external magnetic field. Our detailed efforts on the synthesis of Cu and Fe-based magnetic nanoparticles and their use in Sonagashira-type coupling reactions have been presented as follows.

2.2. Results and Discussion

Initially, superparamagnetic $CuFe_2O_4$ nanoparticles and other ferrite nanoparticles were prepared following the standard co-precipitation method reported earlier.[20] To explore the catalytic activity towards the C(sp)-C(sp2) bond forming reactions, phenylacetylene and iodobenzene was used as the model substrate for the optimization reactions (Scheme 3) (Table 1).

Scheme 3



1

Table 1. Optimization of reaction conditions for coupling between phenylacetylene with iodobenzene

Entry	Catalyst	Solvent	Base	Yield (%)
1	$CuFe_2O_4$	1,4-dioxane	Cs_2CO_3	70
2	$CuFe_2O_4$	DMF	K_2CO_3	≤5
3	$CuFe_2O_4$	DMF	NaOAc	≤5
4	$CuFe_2O_4$	DMF	Cs_2CO_3	35
5	$CuFe_2O_4$	DMF	$NaHCO_3$	≤5
6	$CuFe_2O_4$	DMF	^tBuOK	38
7	$CuFe_2O_4$	1,4-dioxane	^tBuOK	25
8	$CuFe_2O_4$	DMSO	^tBuOK	25
9	$CuFe_2O_4$	CH_3CN	^tBuOK	38
10	$CuFe_2O_4$	^tBuOH	^tBuOK	0

Continued..

11	$CuFe_2O_4$	Toluene	^tBuOK	15
12	$CuFe_2O_4$	THF	^tBuOK	≤5
13	$CuFe_2O_4$	DMF	pyridine	≤5
14	$CuFe_2O_4$	1,4-dioxane	Et_3N	≤5
15	Fe_3O_4	DMF	^tBuOK	0
16	$CoFe_2O_4$	DMF	^tBuOK	0
17	$NiFe_2O_4$	DMF	^tBuOK	8
18	CuO	1,4-dioxane	Cs_2CO_3	25

Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of iodobenzene, 10 mol % of catalyst, 2.0 equiv of base, 5 mL of solvent, 24 h reflux under N_2 atmosphere.

When Fe_3O_4 nanoparticles were employed as the catalyst and the reaction was carried out in DMF using ^tBuOK as base, no reaction takes place. Similarly, on changing the catalyst to $CoFe_2O_4$ the reaction did not proceed. But refluxing the reaction in DMF with $NiFe_2O_4$ nanoparticles, small amount of (8 %) diphenylacetylene **1** was obtained. Formation of **1** is evident from the ^1H and ^{13}C NMR spectra. For example, in ^1H NMR, appearance of multiplet peak at δ 7.58-7.32 and 5 line signal in ^{13}C NMR spectra confirm the formation of **1**. Interestingly, when $CuFe_2O_4$ nanoparticles were applied for the above coupling reactions and the reaction was refluxed in 1,4-dioxane using Cs_2CO_3 as the base, diphenylacetylene was obtained in good yield (70 %) (Table 1, entry 1), whereas, only CuO resulted 25 % of **1**.

Encouraged by the above results, we continued our screening experiments toward the optimization of base. Among the screened bases, Cs_2CO_3 gave the highest yield of **1**. Other bases like K_2CO_3, NaOAc, $NaHCO_3$, Et_3N were found to be ineffective, resulting very low yield of the product. When the reaction mixture was refluxed in DMF using ^tBuOK, only 38 % of the diphenylacetylene was obtained.

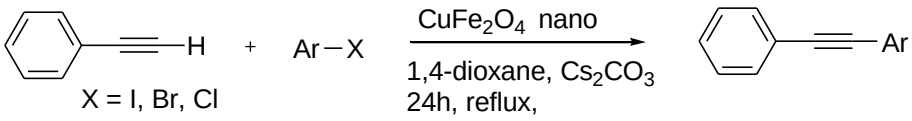
To determine the effect of solvent for the coupling reactions between the phenylacetylene and iodobenzene, a series of experiments were conducted in different solvents. It was found that non polar solvents like toluene have less effect towards the product formations. Changing to polar solvents like ^tBuOH or 1,4-dioxane with ^tBuOK base, either the reaction did not result any product or very low yield of the product was obtained. But refluxing the reaction in acetonitrile,

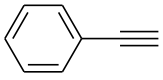
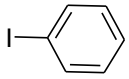
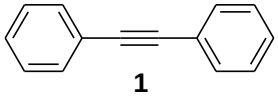
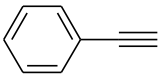
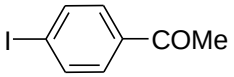
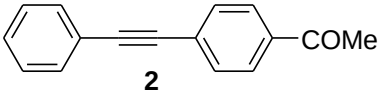
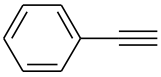
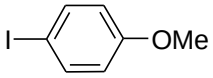
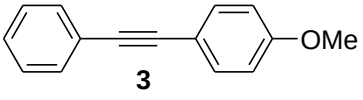
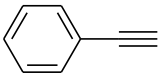
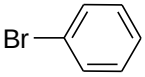
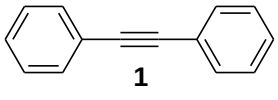
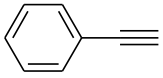
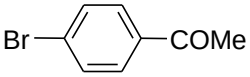
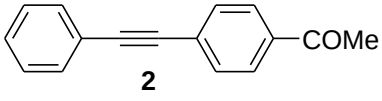
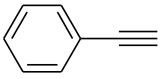
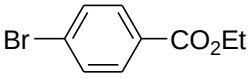
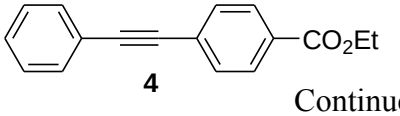
only 38 % of diphenylacetylene was formed. When the reaction was conducted in refluxing 1,4-dioxane using Cs_2CO_3 as the base, optimum yield (70 %) of **1** was isolated.

Substrate Scope

The scope of the cross-coupling reactions was explored by employing $CuFe_2O_4$ nanoparticles as the catalyst. Under the optimized conditions (10 mol % $CuFe_2O_4$, 2.0 equiv. of Cs_2CO_3, 1,4-dioxane, reflux) the coupling between terminal alkynes with several aryl halides underwent smoothly to afford the corresponding product in moderate to good yield (Table 2). For instance, the coupling of phenylacetylene with 4-iodoacetophenone, resulted 48 % of **2**. Similarly, the coupling between deactivated aryl iodides such as 4-iodoanisole with phenylacetylene resulted the cross-coupled product **3** in 51 % yields.

Table 2. $CuFe_2O_4$ nanoparticles catalyzed cross-coupling between terminal alkynes with aryl halides



Entry	Alkyne	Aryl halide	Product	Yield (%)
1			 **1**	70
2			 **2**	48
3			 **3**	51
4			 **1**	58
5			 **2**	35
6			 **4**	42

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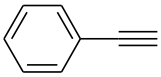
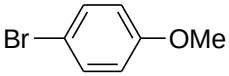
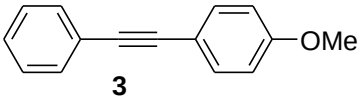
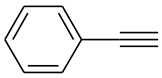
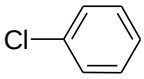
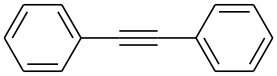
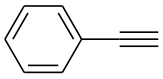
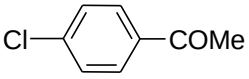
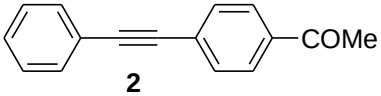
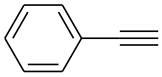
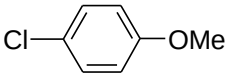
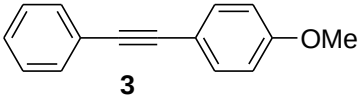
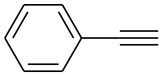
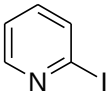
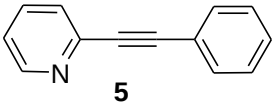
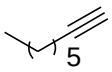
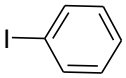
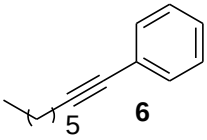
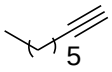
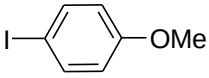
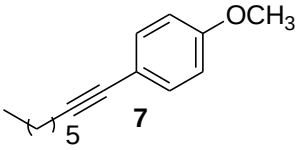
Entry	Alkyne	Aryl halide	Product	Yield (%)
7			 **3**	48
8			 **1**	20
9			 **2**	25
10			 **3**	25
11			 **5**	58
12			 **6**	65
13			 **7**	55

Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of aryl halide, 10 mol % of $CuFe_2O_4$ nanoparticles, 2.0 equiv of Cs_2CO_3, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

The coupling reaction was also extended to aryl bromides and the coupling products were only formed by addition of KI to the reaction mixture containing phenylacetylenes and aryl bromides. This may be due to the halogen exchange between bromine and iodine. When the reaction mixture containing phenylacetylene, bromobenzene and KI was refluxed in 1,4-dioxane for 24 h under nitrogen atmosphere, 58 % of diphenylacetylene was formed. Similarly, the coupling between deactivated aryl bromides such as 4-bromoacetophenone and 4-bromoethylbenzoate with phenylacetylene resulted the corresponding product in 35-42 % yield (Table 2, entries 5, 6). In case of 4-bromoanisole, 48 % of the product **3** was obtained (Table 2,

entry 7). This catalytic system has also found application towards the coupling of aryl chlorides with phenylacetylene, albeit in lower yield even after addition of KI (Table 2, entries 8, 9, 10).

Then, we turned our attention toward the coupling of aliphatic alkynes with aryl iodides. Thus, when we coupled the octynes with iodobenzene using 10 mol % of catalyst under optimized conditions, product **6** was obtained in 65 % yield. Similarly, reactions of octynes with 4-iodoanisole resulted the product **7** in good yield.

2.3. Reusability of the catalyst

To test the efficiency of our catalytic system, we have studied the reusability of the copper ferrite nanoparticles. Since the $CuFe_2O_4$ nanoparticles were magnetic in nature, these were recovered very easily by an external magnet. Then the catalyst was washed with ethyl acetate and acetone, and was dried in a hot air oven at 120 °C for 2 h. The recovered catalyst was now reused under similar conditions for the subsequent cycles. It has been observed that the catalytic behavior of the $CuFe_2O_4$ nanoparticles was found to be almost unaltered (yield, 68 %), even up to three consecutive cycles. Then, the possibility of Cu and Fe leakage from $CuFe_2O_4$ to the medium during the reaction was also investigated. After completion of the reaction, the supernatant was collected and tested for Cu and Fe by atomic absorption spectroscopy (AAS). The leaching of Cu and Fe in three consecutive cycles was found to be ≤0.5 ppm (Table 3), which is well below the permissible level.

Table 3. Reusability of $CuFe_2O_4$ nanoparticles and leaching of Cu and Fe in multicycle C-C coupling reactions.

Cycle	Recovered $CuFe_2O_4$ (%)	Product yield(%)[a]	Cu leakage (ppm)	Fe leakage (ppm)
1	-	70	0.35	0.06
2	97	68	0.3	0.02
3	95	68	0.2	0.02

Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of iodobenzene, 10 mol % of $CuFe_2O_4$ nanoparticles (for cycle 1 and the remaining recovered amount of the catalyst was used for subsequent cycles), 2.0 equiv of Cs_2CO_3, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

2.4. Conclusion

For the first time, we have demonstrated a ligand-free heterogeneous magnetic catalytic system for the cross-coupling of terminal alkynes with aryl halides. The synergistic effects of copper and iron in copper ferrite nanoparticles for the alkynylation reactions were exploited. The reusability and negligible leaching of Cu and Fe from copper ferrite catalysts make the catalytic process attractive and environment benign.

2.5. Experimental

Preparation of copper ferrite nanoparticles

$CuFe_2O_4$ nanoparticles of size 10-25 nm were prepared by co-precipitation of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in water in presence of sodium hydroxide. Briefly, to a solution of $Fe(NO_3)_3.9H_2O$ (3.34 g, 8.2 mmol) and $Cu(NO_3)_2.3H_2O$ (1g, 4.1 mmol) in 75 ml of distilled water, 3 g (75 mmol) of NaOH dissolved in 15 ml of water was added at room temperature over a period of 10 min. during which reddish-black precipitate was formed. Then the reaction mixture was warmed to 90°C and stirred. After 2h, it was cooled to room temperature and the magnetic particles so formed were separated by a magnetic separator, washed with water (3 x 30 ml) and catalyst was kept in air oven for overnight at 80 °C. Then the catalyst was grinded in a mortar-pestle and kept in a furnace at 700 °C for 5 h (step up temperature 20 °C/min). Then it was cooled to room temperature slowly and gave 820 mg of magnetic $CuFe_2O_4$ particles of size 10-25 nm.

Characterization of $CuFe_2O_4$ nanoparticle

The crystal structure and phase purity of the synthesized $CuFe_2O_4$ nanoparticle is determined by XRD (Fig. 1) recorded in Expert Pro Phillips X-ray diffractometer.

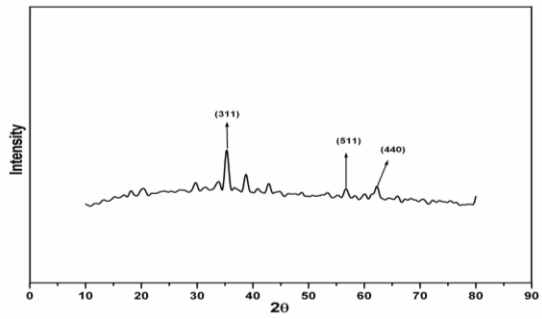


Fig.1. X-ray diffraction pattern of $CuFe_2O_4$ nanoparticles

All the reflection peaks can be easily indexed to crystalline cubic spinel structure of $CuFe_2O_4$ (JCPDS No. 77-0010). The peaks appear at $2\theta = 35.5^o$, 53.5^o and 57.1^o which are well indexed to the crystal plane of spinel ferrite (311), (511) and (440) respectively. The broadening of the peak is due to nanocrystalline nature of the synthesized ferrite nanoparticle.

The morphology and microstructure of synthesized ferrite nanoparticle were analysed by high resolution transmission electron microscopy (JEOL 3010, Japan) operated at 300 kV. The particle size from TEM micrographs was analysed using image J software. Ferrite particles are found to be cubic, well dispersed (Fig. 2a,c) and have a narrow size distribution between 11 and 24 nm with maximum population at 15 nm (Fig. 2b). The high crystallinity of the sample is confirmed by the obvious lattice fringe (Fig. 2d) shown in high resolution TEM. The inter planner distance d is calculated from the image as 1.57 A^o which corresponds to reflection of the [511] plane.

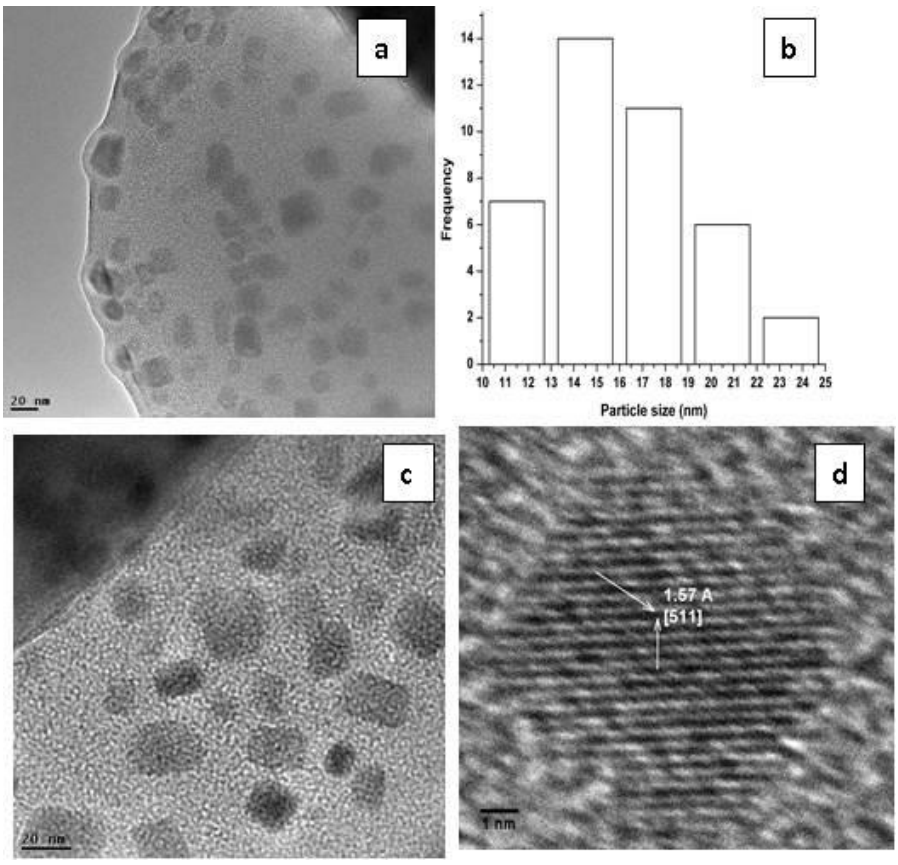
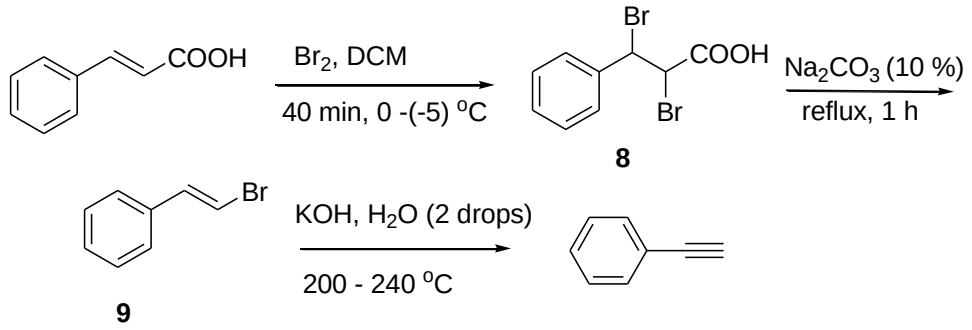


Fig. 2. (a) TEM image of cubic $CuFe_2O_4$ nanoparticles; (b) Particle size distribution histogram; (c) TEM image at higher magnification; (d) HRTEM of a single $CuFe_2O_4$ particle

Preparation of phenylacetylene from cinnamic acid [21]

Phenylacetylenes were prepared following a standard reported procedure from cinnamic acids as shown below.

Scheme 4



Cinnamic acid (37 g, 0.25 mol) was dissolved in a hot dichloromethane (170 mL) in a 250 mL conical flask and was cooled in ice-water bath. As soon as the solid start precipitated, a solution of bromine (40 g, 0.25 mmol) in dichloromethane (30 mL) was added rapidly in three portions and the resulting solution was shaked throughly in ice-water bath for 30 minutes. The solution was then stand in ice-water bath for another 10 minutes and the product **8** was precipitated. The product was collected by filtration. The crude product **8** was then refluxed in 10% Na_2CO_3 solutions (375 mL) for 1 h, cooled to room temperature and the organic layer was collected by ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to get crude *β*-bromostyrene **9**.

50 g of KOH pallets was kept in a 100 mL two neck round bottom flask and 2 drops of water was added. The flask was fitted with a dropping funnel and condenser for downward distillation. The flask was heated in oil bath to 200 ^oC and *β*-bromostyrene **9** was added slowly dropwise by the dropping funnel at a rate of 1 drop in one second. Phenylacetylene slowly distil over and gradually increase the bath temperature to 220 ^oC until the addition of *β*-bromostyrene was completed. Increase the bath temperature to 240 ^oC until no more product distill over. Phenyl acetylene was distilled over in 12.5 g (49 %) as colourless liquid.

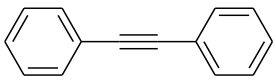
General procedure for the synthesis of aryl iodides from aryl amines[22]

A mixture of aromatic amines (10 mmol), water (1.0 mL) and *p*-TsOH (30 mmol) was grinded in a mortar pastle for 5 minutes. To the above paste, $NaNO_2$ (25 mmol) was added and grinded for another 10 minutes. After completion of the diazotization reactions (tested by β-naphthol) KI (25 mmol) was added and grinding was continued for another 20 minutes. The volume of the paste was increased due to elimination of nitrogen. The crude aryl iodide was then remain as a precipitate by addition of water and aq. Na_2SO_3 solution and was filtered. The crude aryl iodide was purified by column chromatography to get the pure aryl iodide.

General procedure for the arylation of terminal alkynes

To a stirred solution of terminal alkynes (1 equiv), aryl halides (1.52 equiv), and Cs_2CO_3 (2 equiv) in dry 1,4-dioxane, $CuFe_2O_4$ nanoparticles (10 mol %) was added and heated under reflux for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and catalyst was separated by magnetic separator. The catalyst was washed with ethyl acetate. The combined ethyl acetate layer was washed with water (thrice), dried over anhydrous Na_2SO_4, and concentrated to yield the crude product, which was further purified by silica gel column chromatography using petroleum ether / ethyl acetate as eluent to yield the desired product **1-7**.

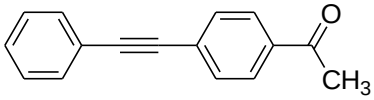
1,2-Diphenylethylene (1)[23]



Following the general procedure, the reaction mixture containing phenylacetylene (100 mg, 1.02 mmol) and iodobenzene (308 mg, 1.52 mmol) was refluxed in dry 1,4-dioxane to afford 121 mg (70 %) of **1** as a colourless solid.

MP: 60-62 °C. IR (KBr): 3054, 2308, 1452, 961 $cm.^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ7.58-7.52 (m, 4H), 7.41-7.32 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6 (d), 128.3 (d), 128.3 (d), 123.2 (s), 89.3 (s). Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66 Found: C, 93.98; H, 5.62.

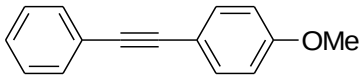
1-(4-(2-Phenylethynyl)phenyl)ethanone (2)[24]



Following the general procedure, the reaction mixture containing phenylacetylene (100 mg, 1.02 mmol) and 4-iodoacetophenone (373 mg, 1.52 mmol) was refluxed in dry 1,4-dioxane to afford 103 mg (48%) of **2** as a colourless solid.

MP: 95-97 °C. IR (KBr): 3058, 2190, 1679, 1602, 1593, 1484, 1442, 1358 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.60 (d, 2H, *J* = 8.4 Hz), 7.56-7.50 (m, 2H), 7.40-7.32 (m, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 136.3, 131.9, 131.8, 129.0, 128.6, 128.4, 128.3, 122.8, 92.9, 88.7, 26.7. Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49, O, 7.26 Found C, 87.12; H, 5.40.

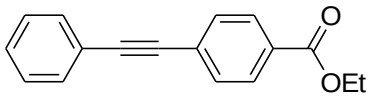
1-(2-(4-Methoxyphenyl)ethynyl)benzene (3) [23]



Following the general procedure, the reaction mixture containing phenylacetylene (100 mg, 1.02 mmol) and 4-iodoanisole (282 mg, 1.52 mmol) was refluxed in dry 1,4-dioxane to afford 104 mg (51%) of **3** as a colourless solid.

MP: 59-60 °C. IR (KBr): 3058, 2185, 1590, 1513, 1440 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.45 (m, 4H), 7.40-7.30 (m, 3H), 6.95-6.80 (m, 2H), 3.85 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (s), 133.0 (d), 131.4 (d), 128.3 (d), 127.9 (d), 123.6 (s), 115.3 (s), 114.0 (d), 89.3 (s), 88.0 (s), 55.3 (q). Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81; O, 7.68 Found C, 86.37; H, 5.92.

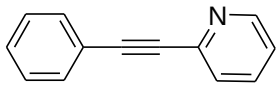
Ethyl 4-(2-phenylethynyl)benzoate (4)



Following the general procedure, the reaction mixture containing phenylacetylene (100 mg, 1.02 mmol) and 2-bromoethylbenzoate (346 mg, 1.52 mmol) was refluxed in dry 1,4-dioxane to afford 103 mg (42%) of **4** as a colourless solid.

MP: 78-79 °C. IR (KBr): 2987, 2213, 1705, 1607, 1560, 1495 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-7.90 (m, 2H), 7.60-7.51 (m, 4H), 7.38-7.32 (m, 3H), 4.39 (q, 2H, *J* = 7.2 Hz), 1.39 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 131.4, 131.1, 129.5, 129.1, 128.4, 128.1, 127.5, 122.6, 92.0, 88.4, 60.8, 14.0. Anal. Calcd. for $C_{15}H_{12}O$: C, 81.58; H, 5.64; O, 12.78 Found C, 81.28; H, 5.34.

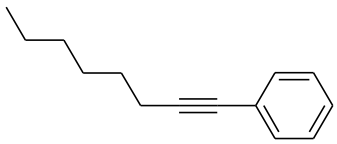
2-(2-Phenylethynyl)pyridine (5)[24]



Following the general procedure, the reaction mixture containing phenylacetylene (100 mg, 1.02 mmol) and 2-iodopyridine (312 mg, 1.52 mmol) was refluxed in dry 1,4-dioxane to afford 102 mg (58%) of **5** as yellow oil.

IR (neat): 2987, 2236, 1595, 1537, 1492 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 1H), 7.62-7.59 (m, 2H), 7.53 (d, 1H, *J* = 8.0 Hz,), 7.38-7.35 (m, 3H), 7.25-7.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 143.8, 136.5, 132.4, 129.3, 128.7, 127.5, 123.1, 122.6, 89.6, 89.0. Anal. Calcd. for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82 Found C, 86.87; H, 4.98; N, 7.86.

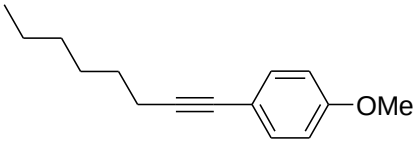
1-(Oct-1-ynyl)benzene (6)[17]



Following the general procedure, the reaction mixture containing octyne (100 mg, 0.90 mmol) and iodobenzene (275 mg, 1.35 mmol) was refluxed in dry 1,4-dioxane to afford 110 mg (65%) of **6** as a colourless oil.

IR (neat): 3072, 2945, 2922, 2247, 1592, 1495, 1468 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.38 (m, 2H), 7.35-7.26 (m, 3H), 2.43 (t, 2H, *J* = 7.2 Hz), 1.68-1.56 (m, 2H), 1.54-1.42 (m, 2H), 1.41-1.30 (m, 4H), 0.93 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5 (d), 128.1 (d), 127.4 (d), 124.1 (s), 90.5 (s), 80.5 (s), 31.4 (t), 28.7 (t), 28.6 (t), 22.6 (t), 19.4 (t), 14.1 (q). Anal. Calcd. for $C_{14}H_8$: C, 90.26; H, 9.74 Found C, 89.92; H, 9.54.

1-Methoxy-4-(oct-1-ynyl)benzene (7)



Following the general procedure, the reaction mixture containing octyne (100 mg, 0.907 mmol) and 4-iodoanisole (318 mg, 1.35 mmol) was refluxed in dry 1,4-dioxane to afford 108 mg (55%) of **7** as a colourless solid.

MP: 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 2H), 6.86-6.80 (m, 2H), 3.81 (s, 3H), 2.40 (t, 2H, *J* = 7.2 Hz), 1.70-1.58 (m, 2H), 1.52-1.40 (m, 2H), 1.38-1.25 (m, 4H), 0.92 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (s), 132.8 (d), 116.3 (s), 113.7 (d), 88.8 (s), 80.2 (s), 55.2 (q), 31.3 (t), 28.8 (t), 28.6 (t), 22.5 (t), 19.4 (t), 14.0 (q). Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32; O, 7.40 Found C, 82.95; H, 9.45.

2.6. References

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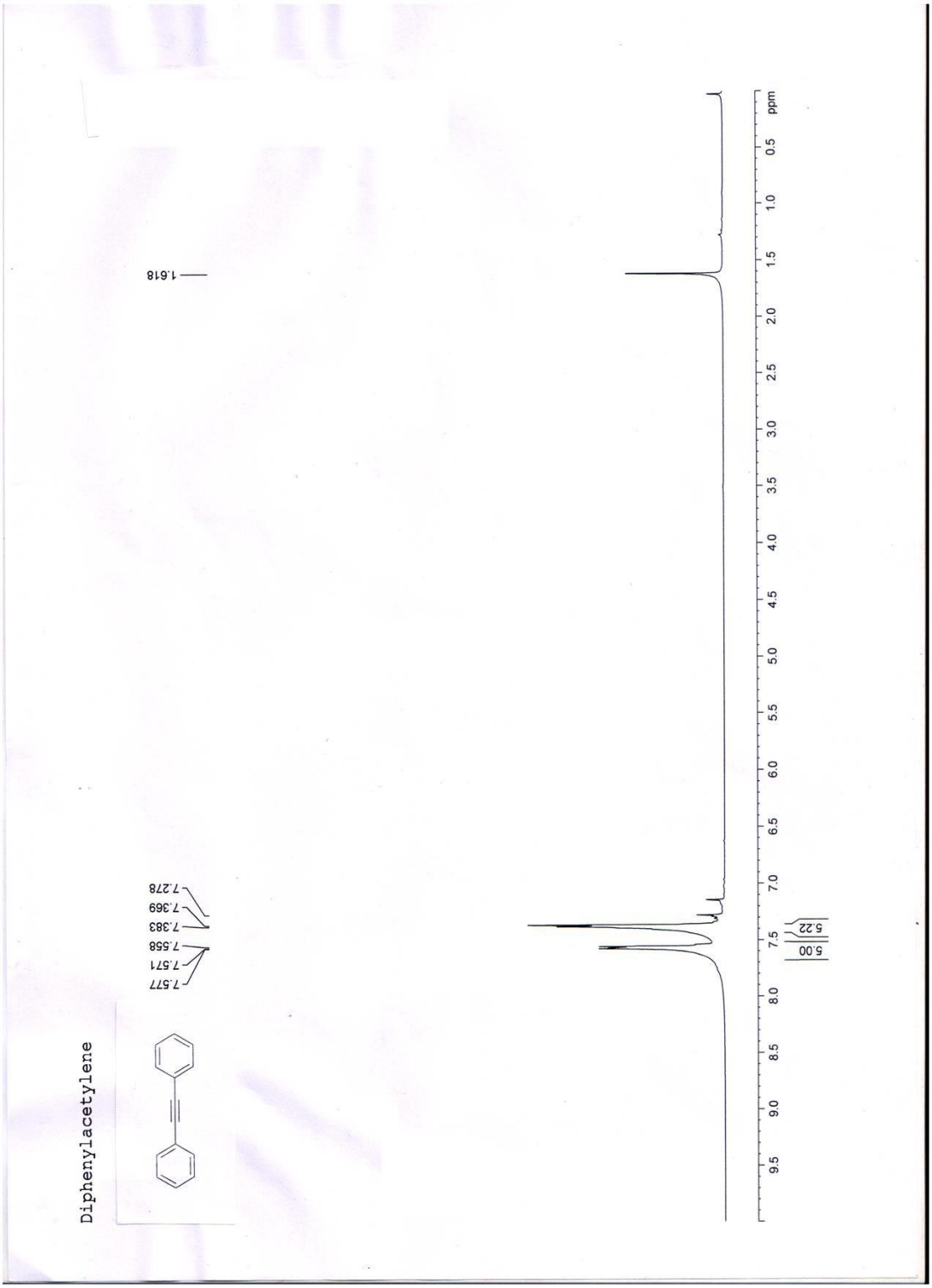
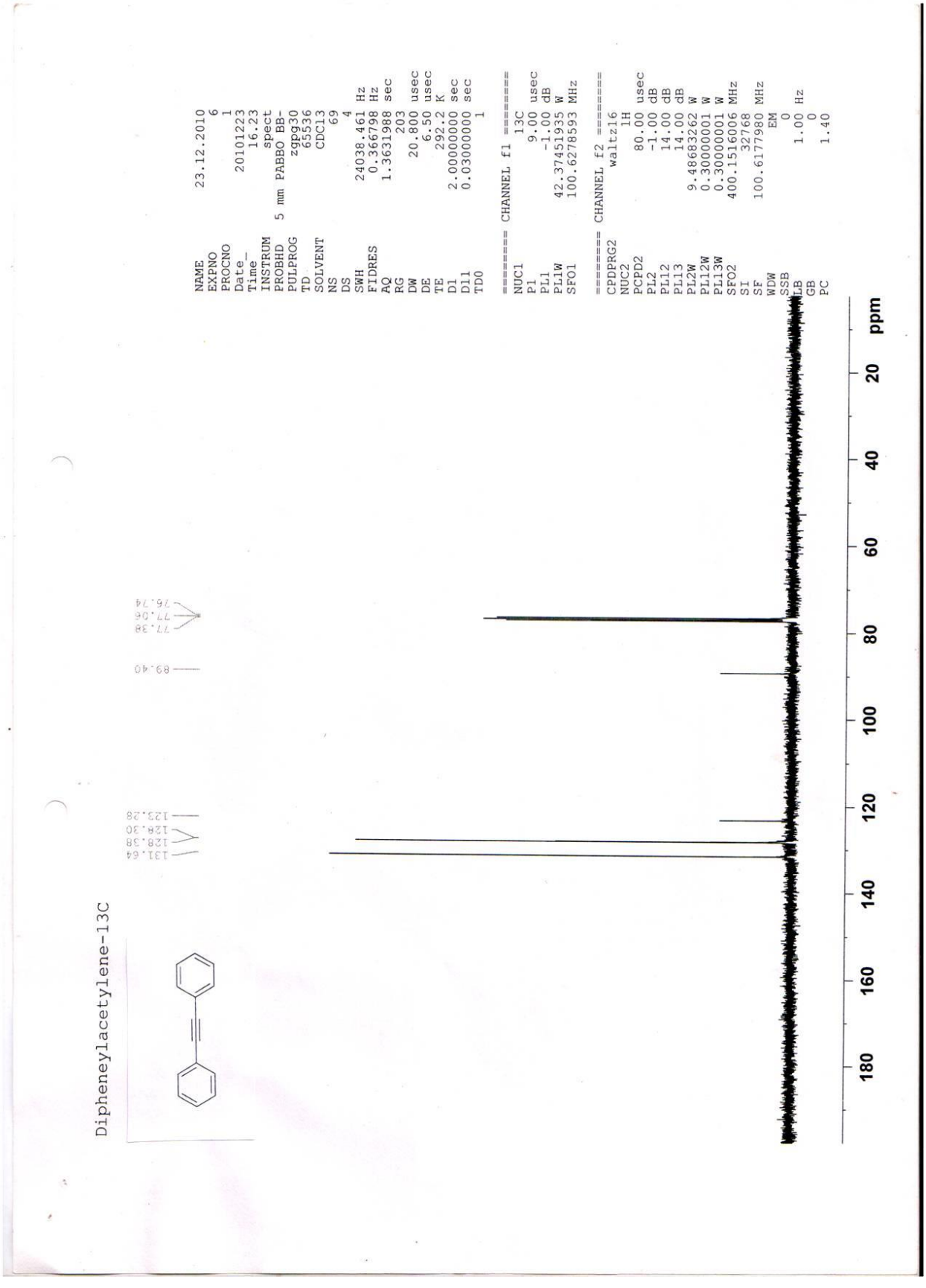
2.7. Selected NMR spectra

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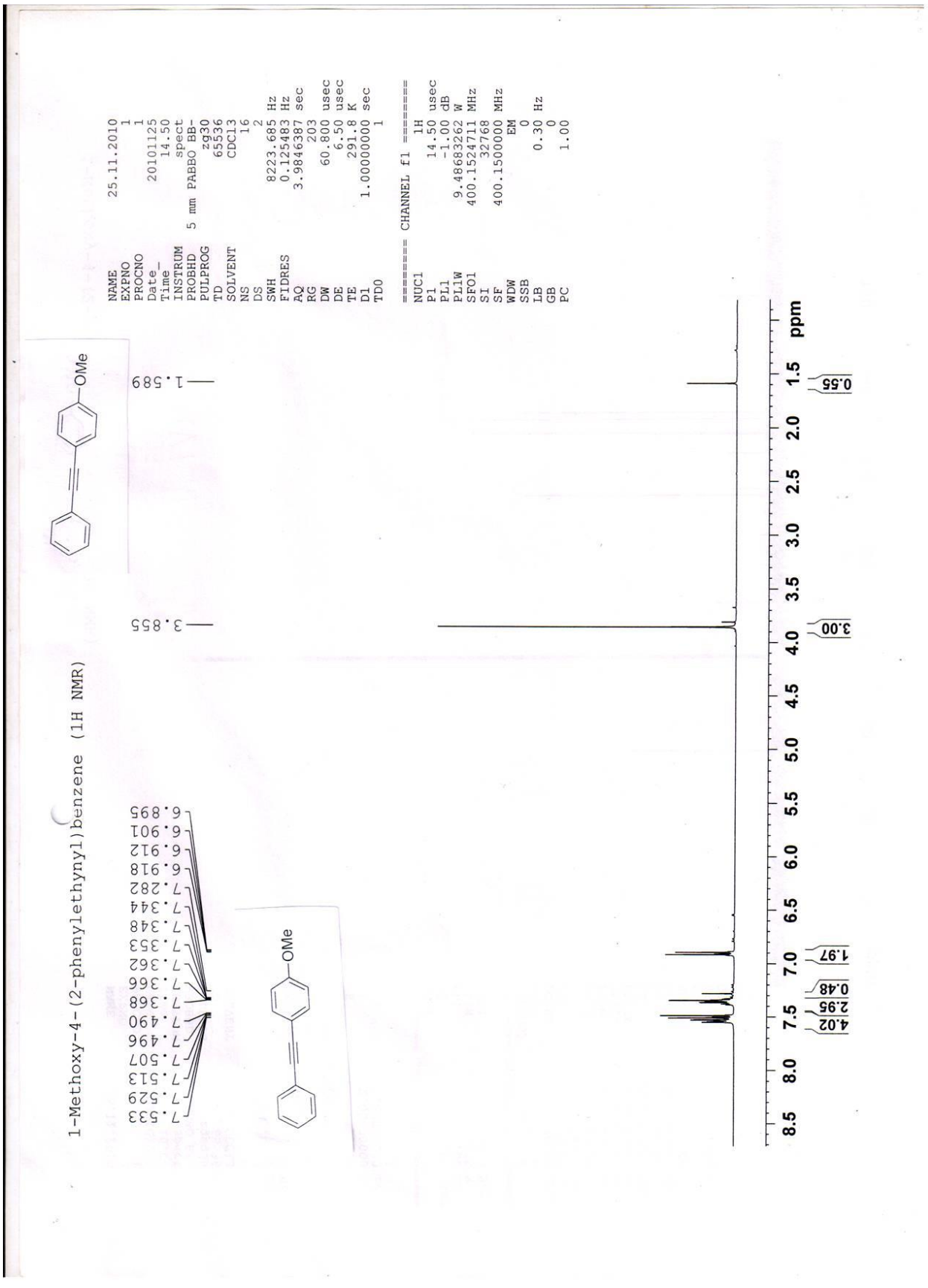
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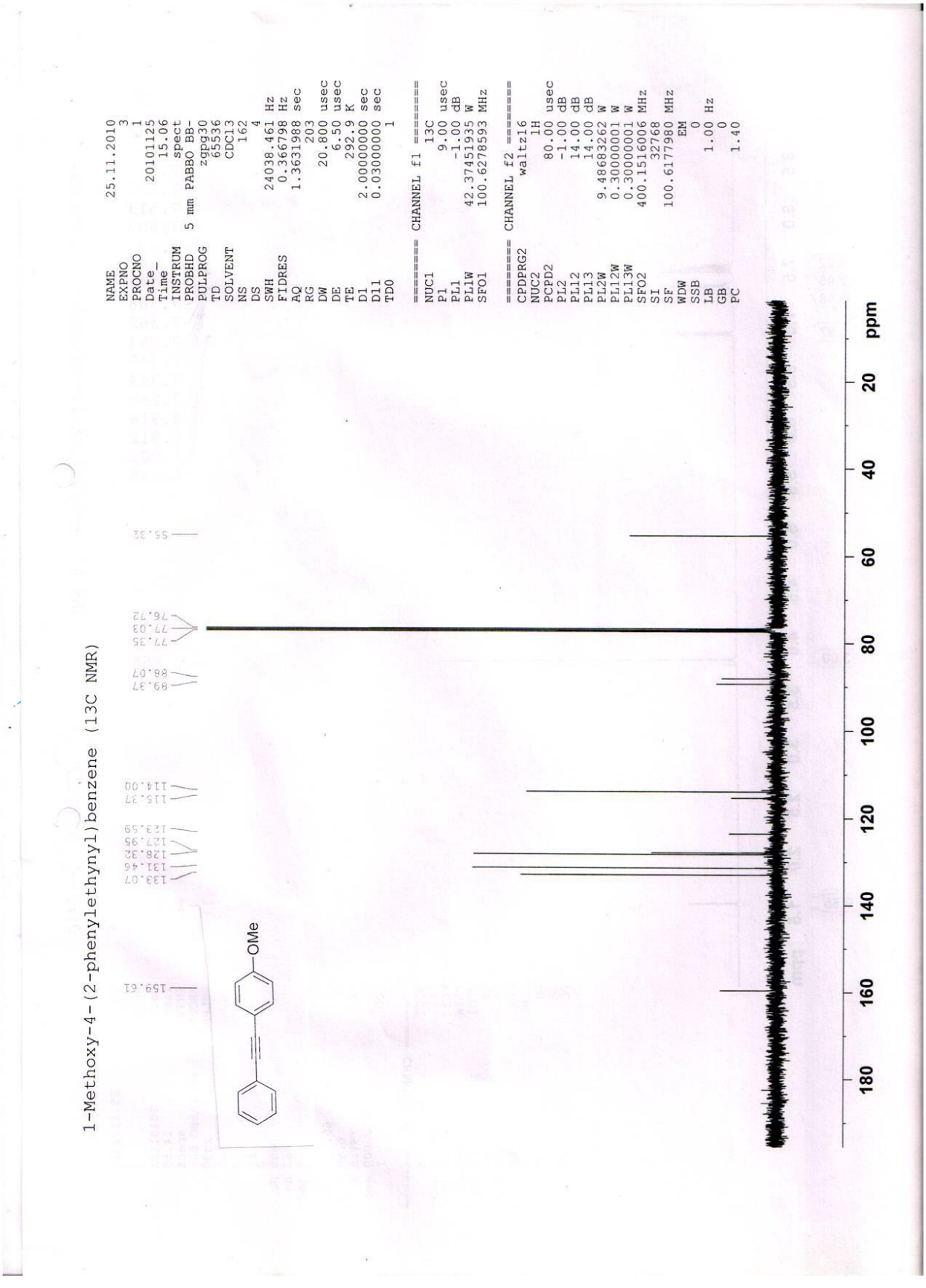
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PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
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PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
159.61
133.07
131.46
128.32
127.95
123.59
115.37
114.00
89.37
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OMe
ppm
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140
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100
80
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40
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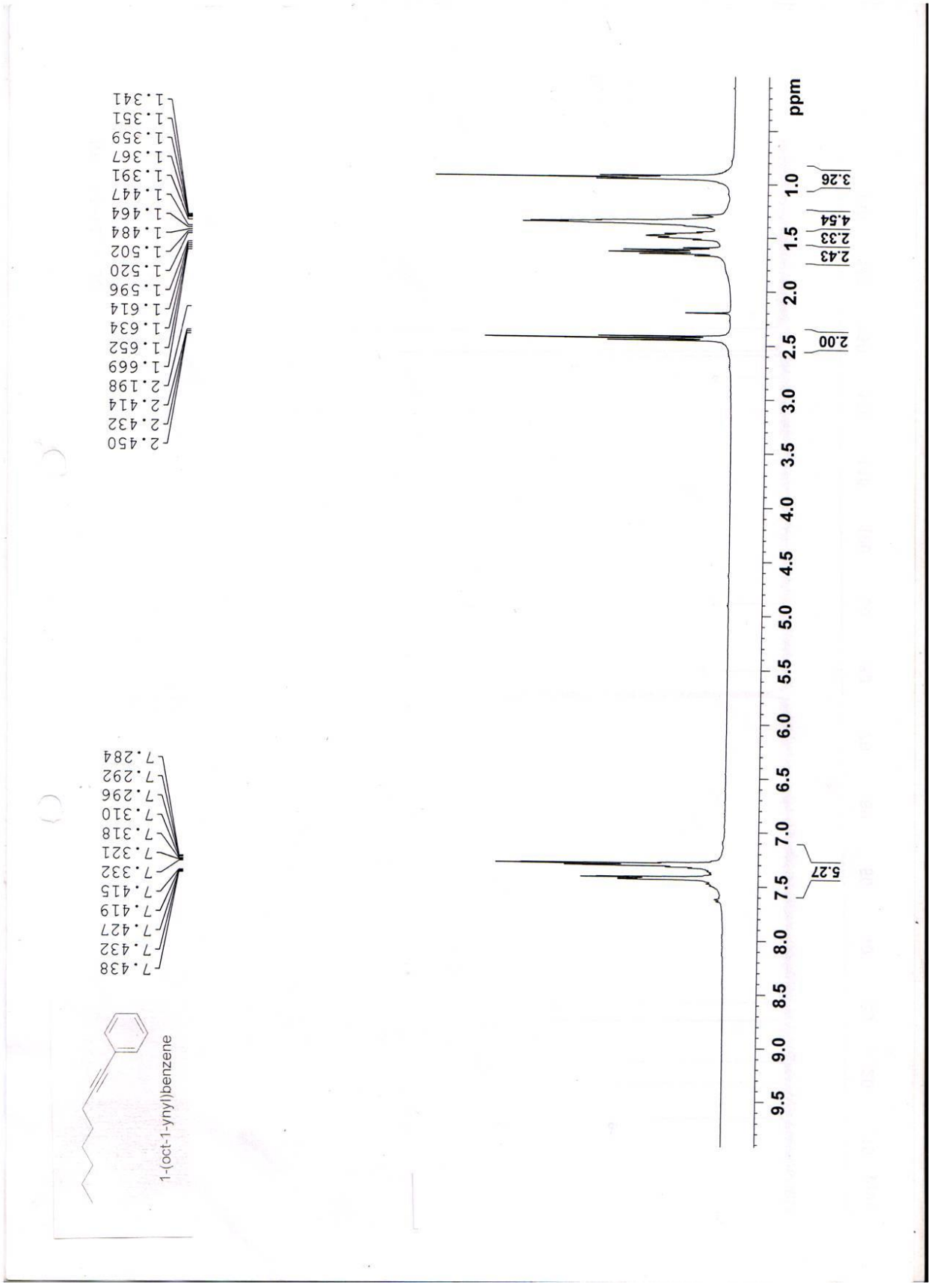
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1.520
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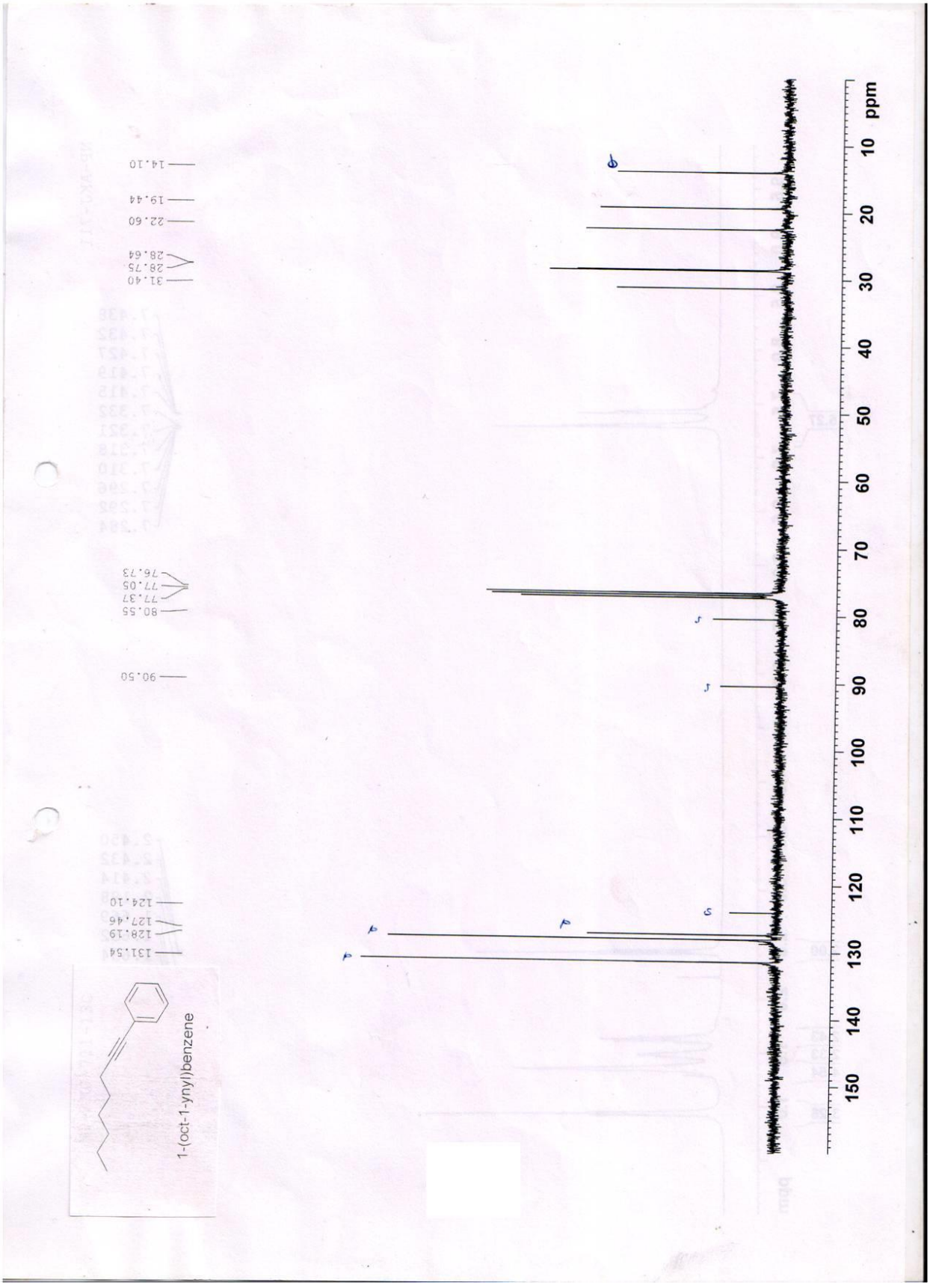
5.27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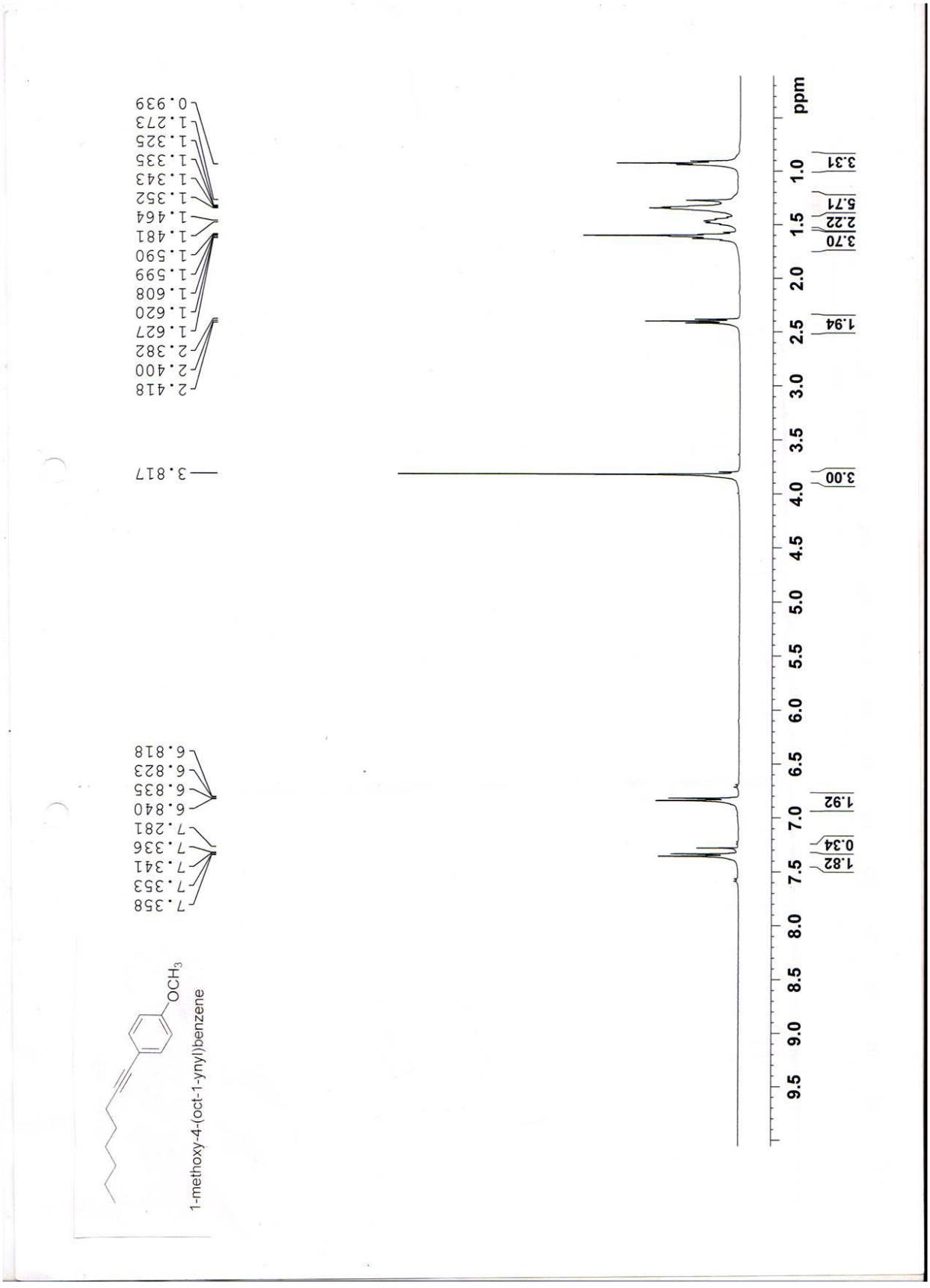
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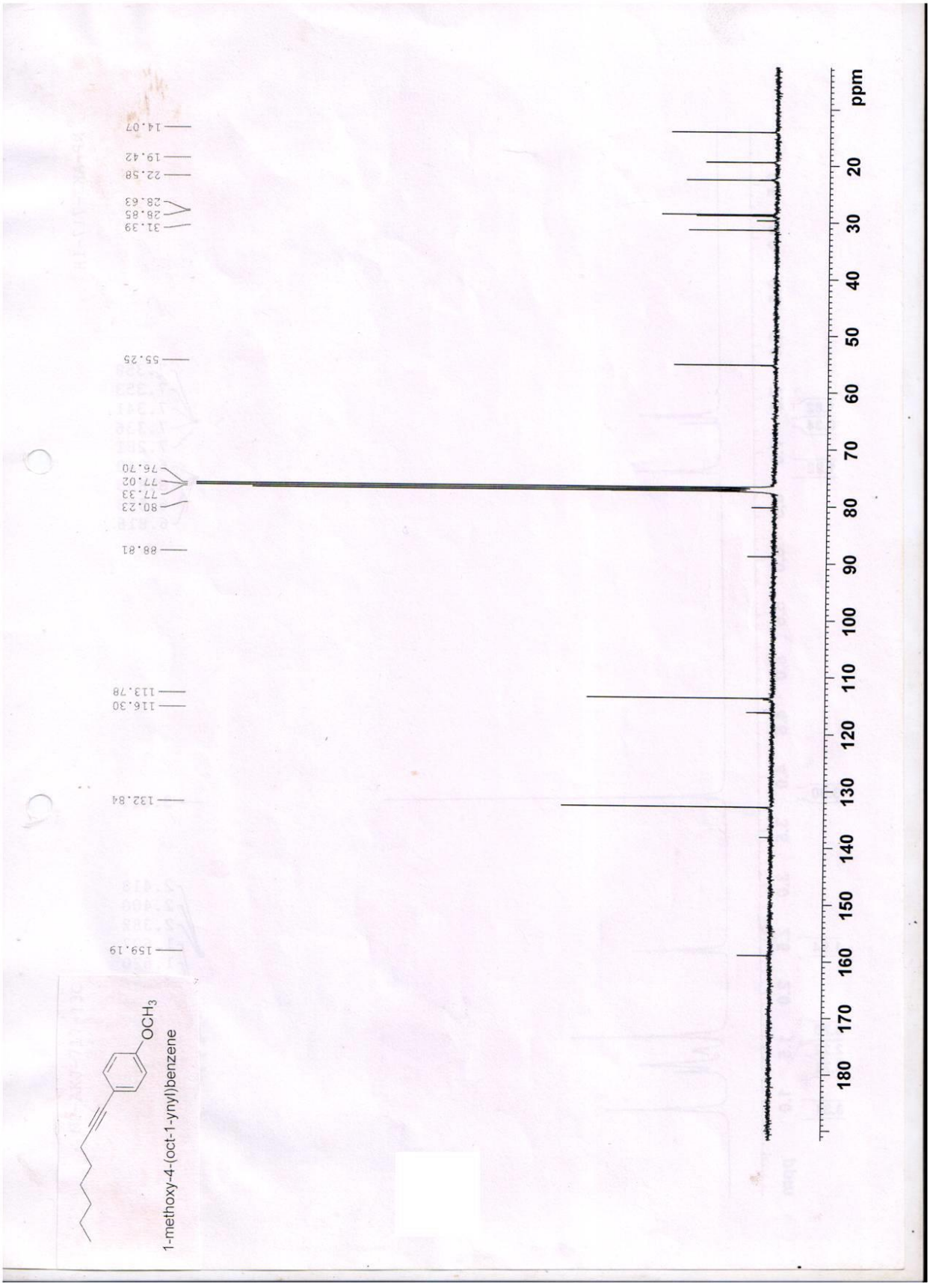
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116.30
132.84
159.19
OCH3
1-methoxy-4-(oct-1-ynyl)benzene
ppm

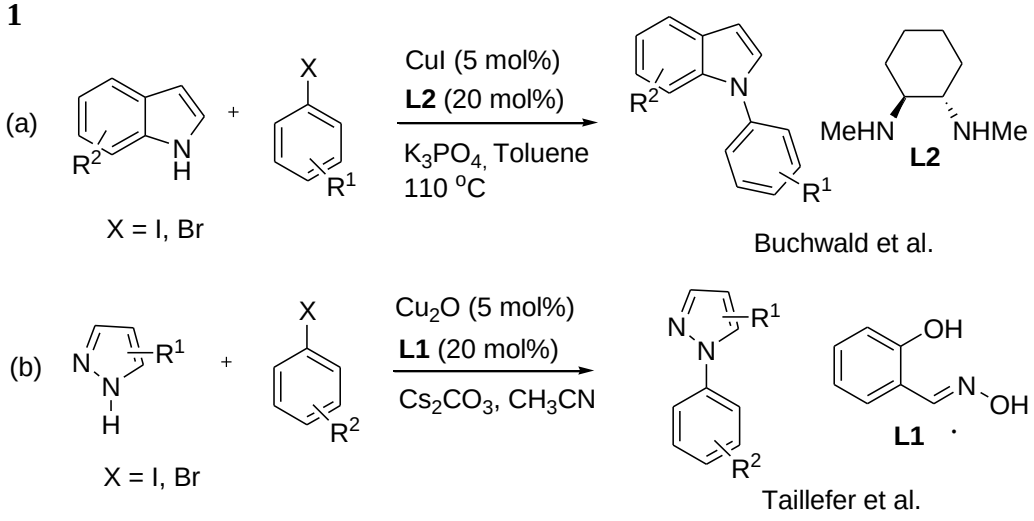
Chapter 3

$CuFe_2O_4$ nanoparticle mediated N-arylation of NH-heterocycles

3.1. Introduction

Since 1903, the copper-catalyzed Ullmann reaction[1] has been widely applied for the N-arylation of nitrogen-containing heterocycles.[2] The classic Ullmann reaction normally requires harsh conditions, such as high temperature (200 °C), stoichiometric amounts of copper and selective halide substrates, which is problematic for industrial use due to high cost and waste disposal. To overcome these drawbacks, recently a number of methods have been developed. Amongst them Chan[3] and Lam[4] illustrated the copper-catalyzed coupling of arylboronic acids with amines and NH-heterocycles. However, the relative instability of boronic acids and the tedious purification procedure limit their further application. Independently, Buchwald[5] and Hartwig[6] employed palladium-based catalysts for the N-arylation of amines with aryl halides. However, toxicity and high cost of Pd catalysts restrict their use on industrial scale. Thus, researchers have turned their attention toward the use of less expensive, less toxic and more efficient metals to replace Pd.[7] Indeed, Buchwald[8] and Taillefer[9] independently made a significant breakthrough in the copper-catalyzed cross-coupling of NH-heterocycles with aryl bromides and iodides in presence of chelating ligands (Scheme 1).

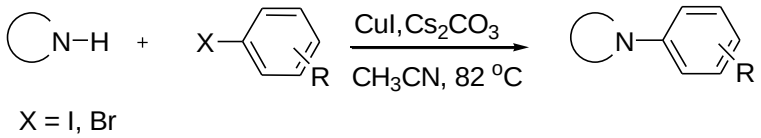
Scheme 1



Subsequently, various nitrogen- and/or oxygen-containing ligands, such as diamines,[10] amino acids,[11] N-hydroxyimides,[12] 1,10-phenanthroline derivatives,[13] pyrrolidine-2-phosphonate,[14] ninhydrin,[15] 8-hydroxy quinoline,[16] 1,3-diketones,[17] etc. have been used as the chelating agents for the N-arylation reactions under homogeneous conditions. Though significant progress has been made in copper-catalyzed C-N cross-coupling reactions, most of the methodology was

restricted to a certain degree owing to the use of expensive and moisture sensitive ligands. From practical and industrial point of view, new methodologies under ligand-free conditions are required. In this respect, ligand-free N-arylation of nitrogen heterocycles reported by Taillefer et al. was encouraging (Scheme 2).[18]

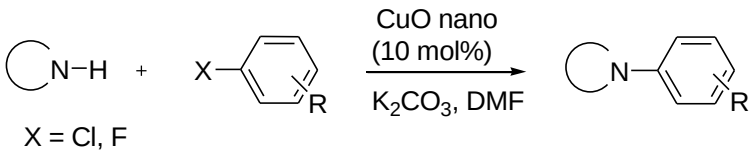
Scheme 2



Later, he demonstrated Cu-Fe co-catalytic route for the N-arylation of NH-heterocycles with aryl bromides at relatively low temperature (90 °C), which was found to be economical and encouraging.[19]

Recently, nanoparticles showed enhanced catalytic activity due to (i) high surface area, (ii) higher zeta potential of the nanoparticles that prevents aggregation compared to bulk material, (iii) low reduction potential that facilitate oxidative addition and (iv) low coordination sites. Due to the above advantage, the nanoparticles were employed for the coupling reactions.[20] Kantam and co-workers exploited the high surface area and reactive morphology of the CuO nanoparticles for the C-N cross-coupling reactions between NH-heterocycles with aryl chlorides and aryl fluorides (Scheme 3).[21]

Scheme 3



Although these results are promising, the small size of nanoparticles often make their separation and recycling difficult, which impedes their use in industrial process.[22] Therefore development of ligand-free, environmental friendly, less expensive and easily separable catalytic system for the N-arylation of heterocycles is still challenging. Inspired by the earlier work reported by Taillefer[19] and Kantam,[21] we envision that magnetically separable copper- and iron-based nanocatalysts with high surface area, whose flocculation and dispersion can be controlled reversibly by application of a magnetic field, may be introduced as a heterogeneous catalyst for

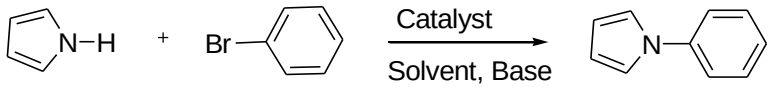
the cross-coupling reactions. In line with our present work (Chapter 2) on $CuFe_2O_4$ nanoparticles mediated C-C cross-coupling reactions between terminal alkynes with aryl halides,[23] we further investigated the catalytic activity of such magnetic nanocatalysts towards the C-N cross-coupling reactions.

In this chapter, we have described the catalytic activity of superparamagnetic copper ferrite ($CuFe_2O_4$) nanoparticles toward the N-arylation of numerous NH-heterocycles with aryl halides under 'ligand-free' conditions.[24]

3.2. Results and Discussion

To evaluate the efficiency of ferrite nanoparticles, pyrrole (**1**) and bromobenzene (**2**) were chosen as the benchmark substrate for the optimization of the N-arylation reactions (Scheme 4) (Table 1). Ferrite nanoparticles were made following the procedure reported in earlier chapter.

Scheme 4



1 **2** **3**

Table 1. N-arylation of pyrrole with bromobenzene in different solvents and bases in presence of different ferrites

Entry	Catalyst	Solvent	Base	Yield (%)
1	$CuFe_2O_4$	DMF	^tBuOK	98
2	$CuFe_2O_4$	DMF	K_2CO_3	35
3	$CuFe_2O_4$	DMF	NaOAc	≤5
4	$CuFe_2O_4$	DMF	Cs_2CO_3	35
5	$CuFe_2O_4$	DMF	$NaHCO_3$	10
6	$CuFe_2O_4$	THF	^tBuOK	00
7	$CuFe_2O_4$	1,4-dioxane	^tBuOK	25
8	$CuFe_2O_4$	DMSO	^tBuOK	38
9	$CuFe_2O_4$	CH_3CN	^tBuOK	25
10	$CuFe_2O_4$	MeOH	^tBuOK	00

Continued..

11	$CuFe_2O_4$	Ethanolamine	^tBuOK	≤5
12	$CuFe_2O_4$	DMF	pyridine	10
13	Fe_3O_4	DMF	^tBuOK	00
14	$CoFe_2O_4$	DMF	^tBuOK	00
15	$NiFe_2O_4$	DMF	^tBuOK	18
16	CuO	DMF	^tBuOK	68
17	$CuFe_2O_4$		^tBuOK	00
18		DMF	^tBuOK	00
19	$CuFe_2O_4$	Toluene	^tBuOK	≤5

Reaction conditions: 1.49 mmol of pyrrole, 1.52 mmol of bromobenzene, 10 mol % of catalyst, 2.0 equiv of base, 5 mL of solvent, 24 h reflux under N_2 atmosphere.

Initially a number of ferrite nanoparticles were employed for above N-arylation reactions. We observed that catalytic amount of Fe_3O_4, and $CoFe_2O_4$ nanoparticles were unable to promote the reactions in DMF using ^tBuOK as the base. On the other hand, we isolated 18 % of the N-phenylpyrrole **3** using $NiFe_2O_4$ nanoparticles (Table 1, entry 15). Formation of **3** is evident from analytical data. For example, in ^1H NMR, the presence of multiplet peak at 6.49-6.40 and 6 line signals in ^{13}C NMR spectrum confirmed the synthesis of N-phenylpyrrole. The yield of the product was increased by applying 10 mol % of CuO as the catalyst in DMF and ^tBuOK as base. Interestingly, $CuFe_2O_4$ nanoparticles showed excellent activity and 98 % of yield was obtained in DMF at 155 °C in presence of 2 equiv. of ^tBuOK (Table 1, entry 1). When we decrease the concentration of the $CuFe_2O_4$ nanocatalysts from 10 mol % to 5 to 1 mol %, decrease in yield of **3** was observed.

The influence of solvents was revealed by conducting a series of experiments. When the reaction was carried out in different polar and non-polar solvents, such as THF, toluene, DMSO, CH_3CN, 1,4-dioxane, ethanolamine and MeOH, under refluxing conditions, only 0-40 % of the N-arylated product was obtained (Table 1, entries 6-11). However, heating the reaction mixture in DMF at its boiling point (153 °C) resulted highest yield of the product (98 %). It was also expected that DMF may chelate the Cu centers in $CuFe_2O_4$ and catalyzed the N-arylation reactions resulting highest yield of **3.**[7d]

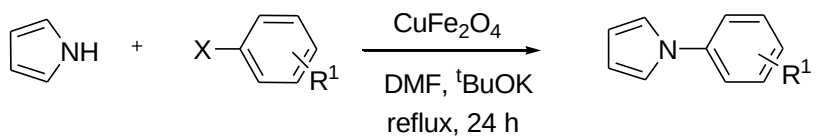
The reactivity of the catalyst in DMF in presence of different bases was also investigated. Among the screened bases (^{t}BuOK, Cs_2CO_3, K_2CO_3, Et_3N, pyridine, $NaHCO_3$, NaOAc), ^{t}BuOK was found to be superior (Table 1).

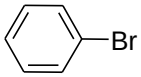
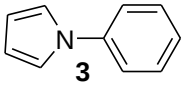
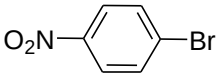
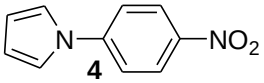
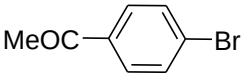
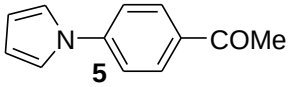
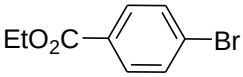
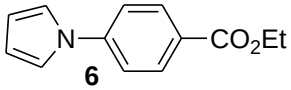
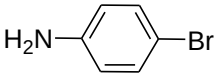
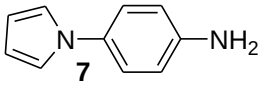
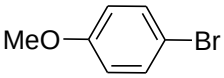
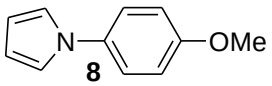
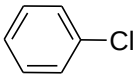
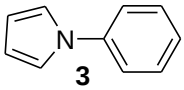
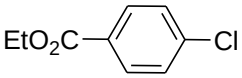
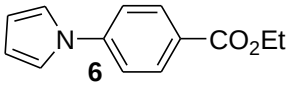
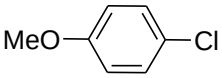
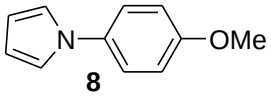
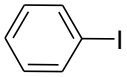
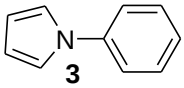
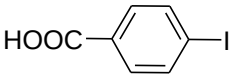
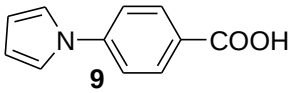
The optimal reaction conditions for the N-arylation of pyrrole with bromobenzene is thus: $CuFe_2O_4$ (10 mol %), ^{t}BuOK (2 equiv), in DMF at 155 $^\circ$C.

Substrate Scope

With the above optimized conditions, we then investigated the scope of the coupling reactions with respect to aryl halides substituted with various electron-withdrawing and –donating substituents using pyrrole as a model NH-heterocycle. When the coupling reaction was carried out between pyrroles with iodobenzene, 99 % of n-phenylpyrrole was obtained (Table 2, entry 10). Similarly, the reactions between pyrrole with 4-iodobenzoic acid resulted the product **5** in 72 % yield (Table 2, entry 11). A decrease in yield was expected due to the decomposition of iodobenzoic acid during the course of reactions. We were delighted to find that the reactions of pyrrole with differently substituted aryl bromides resulted the N-arylated pyrroles in 58-98 % yield (Table 2, entries 1-6). For instance, under optimum reaction conditions, activated aryl bromides such as 4-bromonitrobenzene, 4-bromoacetophenone and 4-bromoethylbenzoate coupled with pyrrole and gave **4**, **5**, **6** respectively (Table 2, entries 2-4). Notably the reactions of deactivated aryl bromides such as 4-bromoanisole and 4-bromoaniline with pyrrole resulted 71 % and 75 % yields, respectively. Furthermore, this catalytic protocol was employed for the N-arylation of pyrroles with less reactive aryl chlorides. Interestingly, the chlorobenzene, 4-chloroethylbenzoate and 4-chloroanisole reacted with pyrrole and gave the coupling product in moderate to good yield. It may be noteworthy that the C–N cross-coupling reactions with aryl chlorides are rarely reported and as mentioned by Taillefer, are significant challenges in Ullmann coupling reactions.[7d]

Table 2. $CuFe_2O_4$ catalyzed C-N cross-coupling of pyrrole with aryl halides



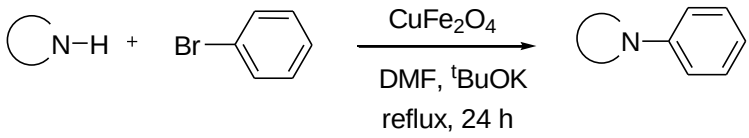
Entry	Aryl halides	Product	Yield[a] (%)
1		 **3**	98
2		 **4**	58
3		 **5**	68
4		 **6**	68
5		 **7**	75
6		 **8**	71
7		 **3**	48
8		 **6**	40
9		 **8**	20
10		 **3**	99
11		 **9**	72

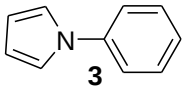
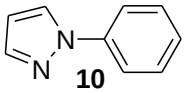
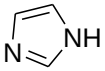
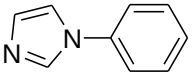
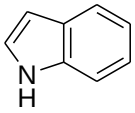
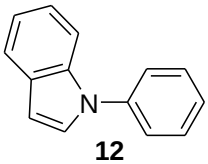
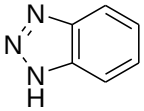
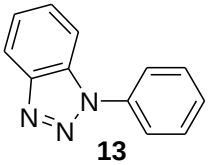
[a] Reaction conditions: 1.49 mmol of pyrrole, 1.52 mmol of aryl halides, 10 mol % of $CuFe_2O_4$ nanoparticles, 2.0 equiv of ^tBuOK, 5 mL of DMF, 24 h reflux under N_2 atmosphere.

We further expanded our methodology toward the N-arylation of other nitrogen containing heterocycles. For example, the coupling of pyrazoles with bromobenzene in DMF

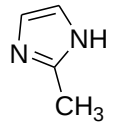
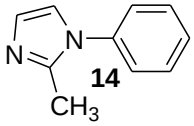
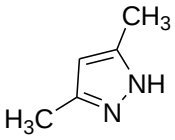
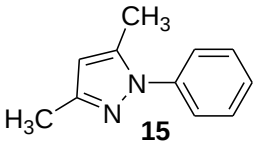
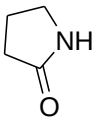
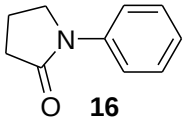
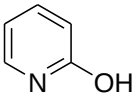
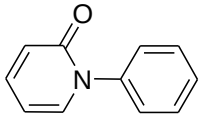
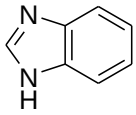
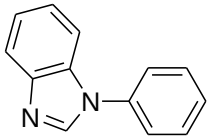
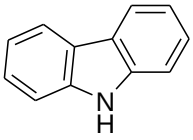
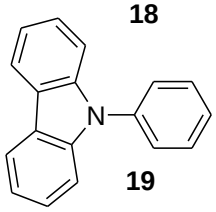
afforded the corresponding N-phenylpyrazole **10** in 97 % yield (Table 3, entry 2). Similarly, other nitrogen containing heterocycles such as imidazoles, benzimidazoles, indoles, carbazoles resulted good to excellent yield of the product (75-90 %) under the optimized conditions (Table 3, entries 3, 4, 10, 11). However, in case of substituted imidazoles and pyrazoles lower yield of **14** and **15** (59 % and 50 % respectively) were obtained. This may be due to the steric hindrance of the reactive site. Interestingly, our optimized conditions showed excellent selectivity towards the N-arylation over the O-arylation as observed in case of 2-pyrrolidone and 2-hydroxypyridine (Table 3, entries 8, 9).

Table 3. $CuFe_2O_4$-catalyzed C-N cross-coupling of NH-heterocycles with bromobenzene



Entry	NH-heterocycles	Product	Yield (%)
1		 **3**	98
2		 **10**	97
3		 **11**	83
4		 **12**	90
5		 **13**	75

Continued..

Entry	NH-heterocycles	Product	Yield (%)
6		 **14**	59
7		 **15**	50
8		 **16**	85
9		 **17**	80
10		 **18**	85
11		 **19**	82

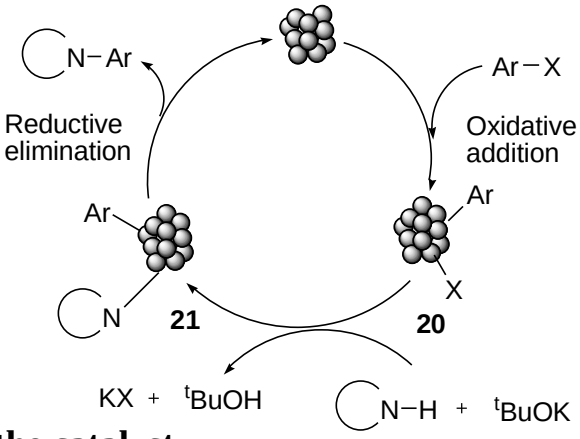
Reaction conditions: 100 mg of azole, 1.02 equiv. of bromobenzene, 10 mol % of $CuFe_2O_4$ nanoparticles, 2.0 equiv of ^tBuOK, 5 mL of DMF, 24 h reflux under N_2 atmosphere.

Plausible Mechanism

It has been observed that the reactivity order of halobenzene is iodobenzene > bromobenzene > chlorobenzene (Table 2, entries 1, 7, 10). Furthermore, in presence of Fe_3O_4 the N-arylation did not take place where as with CuO, 60 % of the N-arylated product was isolated (Table 1, entries 13, 16). Based on these observations it is expected that the C-N cross-coupling reaction may proceed through the oxidative addition followed by reductive elimination pathway. Initially, the copper ferrite nanoparticles undergo oxidative addition to the aryl halides to form

the intermediate **20**, which reacted with NH-heterocycles in presence of ^{t}BuOK to form **21**. Finally, **21** transformed into the N-arylated product by reductive elimination. Due to high surface area and easier transfer of electrons, the copper ferrite nanoparticles may facilitate the oxidative addition reactions and also the polar DMF may prevent the aggregation of the nanoparticles and hence increases the catalyst solubility and stability during the reactions (Scheme 5).[20]

Scheme 5



3.3. Reusability of the catalyst

The reusability of the $CuFe_2O_4$ nanoparticles for the N-arylation was also studied (Table 4). Since the $CuFe_2O_4$ nanoparticles are magnetic in nature, these can be recovered from the reaction mixture using a simple external magnet after completion of the reaction. The recovered catalyst was washed with ethyl acetate followed by acetone and then dried in a hot air oven at 120 $^{\circ}$C for 2 h. The recovered catalyst was reused under similar reaction conditions for subsequent run and the catalytic behavior of the $CuFe_2O_4$ nanoparticles was found to be unaltered (yield >95%), even up to three consecutive cycle.

Table 4.

Cycle	Recovered $CuFe_2O_4$ (%)	Product yield (%)	Cu leakage (in ppm)	Fe leakage (in ppm)
1		98	0.45	0.08
2	97	96	0.4	0.02
3	95	96	0.2	0,02

Reaction conditions: 1.49 mmol of pyrrole, 1.52 mmol of bromobenzene, 10 mol % of $CuFe_2O_4$ nanoparticles (for cycle 1 and the remaining recovered amount of the catalyst was used for subsequent cycles), 2.0 equiv of ^{t}BuOK, 5 mL of DMF, 24 h reflux under N_2 atmosphere.

3.4. Conclusion

For the first time, we have explored the catalytic activity of copper ferrite nanoparticles for the C-N cross-coupling reactions between NH-heterocycles with differently substituted aryl halides. A wide range of NH-heterocycles such as pyrroles, imidazoles, pyrazoles, benzimidazoles, indoles, carbazoles, substituted pyrazoles and substituted imidazoles etc. have been arylated efficiently. Our methodology could tolerate an array of functional groups such as nitro, ester, methoxy, ketone and free primary amines on the aryl halides. The magnetic nature of $CuFe_2O_4$ nanoparticles is particularly advantageous for easy, rapid and quantitative separation of the catalyst for reuse. This catalytic process is simple, efficient, economical and environmentally safe towards the N-arylation of nitrogen containing heterocycles.

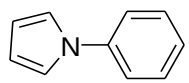
3.5. Experimental

General Procedure for N-arylation reactions

To a solution of NH-heterocycle (1 equiv.), bromobenzene (1.02 equiv.) and ^{t}BuOK (2 equiv.) in dry DMF, $CuFe_2O_4$ (10 mol %) was added and heated at reflux for 24 h under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with ethyl acetate and catalyst was separated by magnetic separator. The catalyst was washed with ethyl acetate. The combined ethyl acetate layer was washed with water (twice), dried over anhydrous Na_2SO_4 and concentrated to yield the crude product, which was further purified by silica gel column chromatography using petroleum ether / ethyl acetate as eluent to yield the N-arylated product **3-19**.

For reusability study, the catalyst so separated by magnetic separator was washed with ethyl acetate (twice) followed by distilled water and acetone. Then it was dried in hot air oven at 120° C for 2 h and reused. The catalyst was reused for *N*-arylation of pyrrole only.

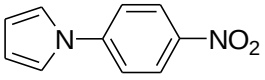
1-Phenyl-1H-pyrrole (3)



Following the general procedure 1*H*-pyrrole (1 g, 14.9 mmol) was coupled with bromobenzene (1.61 ml, 15.2 mmol). The crude brown oil was purified by silica gel column chromatography (eluent: petroleum ether) gave 2.02 g (98 %) of the desired product as a colourless solid.

MP: 62 °C (Litt.[19] 60 °C). IR (KBr): 3139, 1601, 1554, 1504, 1457 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.40 (m, 4H), 7.36-7.20 (m, 1H), 7.18-7.10 (m, 2H), 6.49-6.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.79 (s), 129.54 (d), 125.62 (d), 120.55 (d), 119.33 (d), 110.39 (d). Anal. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78; Found: C, 83.79; H, 6.30; N, 9.85.

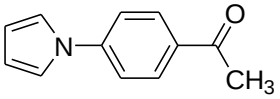
1-(4-Nitrophenyl)-1H-pyrrole (4)



Following the general procedure 1*H*-pyrrole (100 mg, 1.49 mmol) was coupled with p-bromonitrobenzene (300 mg, 1.52 mmol). The crude compound was purified by silica gel chromatography (eluent: petroleum ether and ethyl acetate) gave 162 mg (58%) of desired product **4** as a white solid.

MP: 178-180 °C (Litt.[25]: 179-180 °C). IR (KBr): 2930, 2855, 1605, 1518, 1487 cm.$^{-1}$. ^{1}H NMR (400 MHz, CDCl3): δ 8.32 (d, *J* = 8.8 Hz, 2H), 7.53(d, *J* = 8.8 Hz, 2H), 7.18 (s, 2H), 6.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.19, 144.67, 125.54, 119.37, 119.03, 112.49. Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89; O, 17.00; Found: C, 63.85; H, 4.26; N, 14.92; O, 16.98.

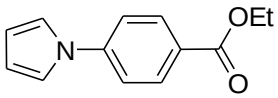
1-(4-(1H-Pyrrol-1-yl)phenyl)ethanone (5)



Following the general procedure 1*H*-pyrrole (100 mg, 1.49 mmol) was coupled with p-bromoacetophenone (302 mg, 1.52 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 9.5:0.5) gave 188 mg (68 %) of the desired product **5** as a white solid.

MP: 119-121 °C. IR (KBr): 3138, 3004, 1679, 1604, 1522, 1471, 1425 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.94 (m, 2H), 7.42-7.38 (m, 2H), 7.12-7.08 (m, 2H), 6.33-6.30 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.74 (s), 144.06 (s), 134.05 (s), 130.18 (d), 119.37 (d), 119.02 (d), 111.61 (d), 26.49 (q). Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56; O, 8.64; Found: C, 77.80; H, 5.95; N, 7.53; O, 8.68. MS (ES) *m/z* (relative intensity) 186 ([M+H],$^{+}$ 100%).

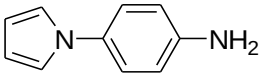
Ethyl-4-(1H-pyrrol-1-yl)benzoate (6)



Following the general procedure 1*H*-pyrrole (100 mg, 1.49 mmol) was coupled with ethyl 4-bromobenzoate (0.25 ml, 1.52 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 9.5:0.5) gave 151 mg (68 %) of the desired product **6** as a white solid.

MP: 73 °C. IR (KBr): 2980, 1711, 1608, 1519, 1475 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.10 (m, 2H), 7.50-7.44 (m, 2H), 7.20-7.16 (m, 2H), 6.42-6.40 (m, 2H), 4.46-4.36 (q, 2H), 1.46-1.40 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.98 (s), 143.93 (s), 131.27 (d), 127.30 (s), 119.30 (d), 119.06 (d), 111.44 (d), 61.07 (t), 14.37 (q). Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51; O, 14.87; Found: C, 72.70; H, 5.96; N, 6.58; O, 14.95. MS (ES) *m/z* (relative intensity) 216 ($[M+H]^+$ 100%).

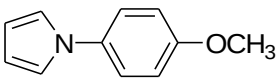
4-(1H-Pyrro-1-yl)benzenamine (7)



Following the general procedure 1*H*-pyrrole (100 mg, 1.49 mmol) was coupled with 4-bromoaniline (261 mg, 1.52 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 9:1) gave 177 mg (75 %) of the desired product **7** as a black solid.

MP: 85-87 °C (Litt.[12]: 86-87 °C). IR (KBr): 3416, 3326, 2920, 1627, 1521, 1398 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.18 (m, 2H), 7.02-6.88 (m, 2H), 6.78-6.70 (m, 2H), 6.34-6.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ144.49 (s), 132.97 (s), 122.40 (d), 119.70 (d), 115.70 (d), 109.45 (d). Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71; Found: C, 75.95; H, 6.39; N, 17.65.

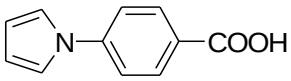
1-(4-Methoxyphenyl)-1H-pyrrole (8)



Following the general procedure 1*H*-pyrrole (100 mg, 1.49 mmol) was coupled with 4-bromoanisole (0.19 ml, 1.52 mmol). The crude compound was purified by silica gel column chromatography (eluent: dichloromethane : petroleum ether) gave 197 mg (71 %) of the desired product **8** as a colourless solid.

MP: 108-110 °C. IR (KBr): 3139, 2960, 2835, 1598, 1523, 1460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 3H), 7.05-6.95 (m, 3H), 6.37-6.33 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.68 (s), 134.49 (s), 122.21 (d), 119.70 (d), 114.63 (d), 109.83 (d), 55.57 (q). Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09; O, 9.24: Found: C, 76.19; H, 6.35; N, 8.15; O, 9.20. MS (ES) *m/z* (relative intensity) 174 ($[M+H]^+$ 100%).

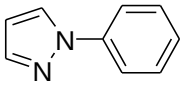
4-(1H-Pyrrol-1-yl)benzoic acid (9)



Following the similar procedure 1*H*-pyrrole (200 mg, 2.98 mmol) was coupled with 4-iodobenzoic acid (369 mg, 1.49 mmol). The crude compound was neutralized by dil. NaOH solution, washed with dichloromethane. The aqueous layer was acidified by conc. HCl, extracted with ethyl acetate, gave 201 mg (72 %) of desired product **9** as a black solid.

MP: 200 °C (Litt.[26]: 199-201°C). IR (KBr): 3439, 1677, 1605, 1522, 1478, 1431 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$:DMSO-d_6 9:1): δ 8.06-7.95 (m, 2H), 7.42-7.36 (m, 2H), 7.14-7.08 (m, 2H), 6.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 9:1): δ 172.35 (s), 148.37 (s), 136.17 (d), 132.57 (s), 123.82 (d), 123.70 (d), 116.11 (d). Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48; O, 17.09; Found: C, 70.51; H, 4.82; N, 7.52; O, 17.14.

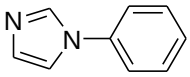
1-Phenyl-1H-pyrazole (10)[19]



Following the general procedure 1*H*-pyrazole (100 mg, 1.47 mmol) was coupled with brombenzene (0.16 ml, 1.49 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 9.5:0.5) gave 205 mg (97 %) of the desired product **10** as a yellow oil.

IR (neat): 3121, 3049, 1598, 1519, 1500, 1462 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.90 (d, 1H), 7.78-7.65 (m, 3H), 7.52-7.40 (m, 2H), 7.35-7.26 (m, 1H), 6.50-6.46 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.07 (d), 140.19 (s), 129.45 (d), 126.79 (d), 126.47 (d), 119.24 (d), 107.61 (d).

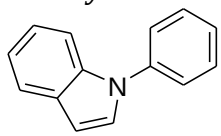
1-Phenyl-1H-imidazole (11)[19]



Following the general procedure 1*H*-imidazole (100 mg, 1.46 mmol) was coupled with bromobenzene (0.16 ml, 1.48 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 8:2) gave 175 mg (83 %) of the desired product **11** as a yellow oil.

IR (neat): 3117, 1599, 1509, 1460 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.42-7.36 (m, 2H), 7.34-7.25 (m, 3H), 7.20 (s, 1H), 7.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.31 (s), 135.56 (d), 130.29 (d), 129.89 (d), 127.52 (d), 121.48 (d), 118.26 (d).

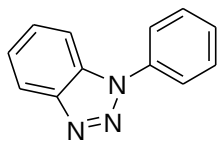
1-Phenyl-1H-indole (12)[19]



Following the general procedure 1*H*-indole (100 mg, 0.854 mmol) was coupled with bromobenzene (0.09 ml, 0.87 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether) gave 148 mg (90 %) of the desired product **12** as a light green oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.70 (m, 1H), 7.64-7.60 (m, 1H), 7.58-7.50 (m, 4H), 7.42-7.34 (m, 2H), 7.30-7.18 (m, 2H), 6.75-6.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.86 (s), 135.88 (s), 129.63 (d), 129.34 (s), 127.97 (d), 126.46 (d), 124.40 (d), 122.36 (d), 121.14 (d), 120.37 (d), 110.52 (d), 103.58 (d).

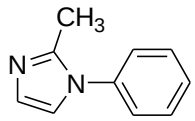
1-Phenyl-1H-benzo-[d][1,2,3]triazole (13)



Following the general procedure 1*H*-benzotriazole (100 mg, 0.84 mmol) was coupled with bromobenzene (0.09 ml, 0.85 mmol). The crude brown oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate) gave 115 mg (70 %) of the desired product **13** as a yellow solid.

MP: 86-88 °C (Litt.[27]: 85-87 °C). IR (KBr): 3060, 2920, 1596, 1553, 1503, 1453 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.06 (m, 1H), 7.75-7.66 (m, 3H), 7.58-7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.02 (s), 133.08 (s), 129.88 (d), 128.70 (d), 128.26 (d), 124.43 (d), 124.21 (s), 122.92 (d), 120.03 (d), 110.38 (d). Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52; Found: C, 73.80; H, 4.67; N, 21.55.

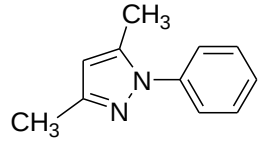
2-Methyl-1-phenyl-1H-imidazole (14)[28]



Following the general procedure 2-methyl-1*H*-imidazole (100 mg, 1.24 mmol) was coupled with bromobenzene (0.13 ml, 1.27 mmol). The crude compound was purified by silica gel column chromatography (petroleum ether : ethyl acetate) gave 114 mg (59 %) of the desired product **14** as a light yellow oil.

IR (neat): 2927, 1598, 1502, 1416 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.38 (m, 3H), 7.30-7.24 (m, 2H), 7.04-6.98 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.67 (s), 137.97 (s), 129.46 (d), 128.17 (d), 127.52 (d), 125.50 (d), 120.62 (d), 13.66 (q).

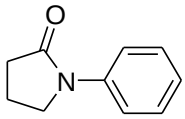
3,5-Dimethyl-1-phenyl-1H-pyrazole (15)[19]



Following the general procedure 3,5-dimethyl-1*H*-pyrazole (100 mg, 1.04 mmol) was coupled with bromobenzene (0.11 ml, 1.06 mmol). The crude black oil was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 90 mg (50 %) of the desired product **15** as a yellow oil.

IR (neat): 2921, 1596, 1554, 1502 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.41 (m, 4H), 7.40-7.32 (m, 1H), 6.02 (s, 1H), 2.36-2.28 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.83 (s), 139.70 (s), 139.48 (s), 129.05 (d), 127.48 (d), 124.84 (d), 106.97 (d), 13.37 (q), 12.34 (q).

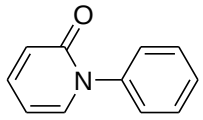
1-Phenylpyrolidin-2-one (16)



Following the general procedure 2-pyrollidone (100 mg, 1.17 mmol) was coupled with bromobenzene (0.12 ml, 1.19 mmol). The crude compound was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 9:1) gave 161 mg (85%) of the desired product **16** as a yellow solid.

MP: 69 °C (Litt.[19]: 68 °C). IR (KBr): 2917, 1680, 1596, 1498, 1460 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (m, 2H), 7.41-7.34 (m, 2H), 7.19-7.12 (m, 1H), 3.88 (t, 2H), 2.63 (t, 2H), 2.22-2.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.25 (s), 139.40 (s), 128.82 (d), 124.52 (d), 119.99 (d), 48.81 (t), 32.76 (t), 18.04 (t). Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; O, 9.93; Found: C, 74.41; H, 6.85; N, 8.72; O, 9.90.

1-Phenylpyridin-2-(1H)one (17)

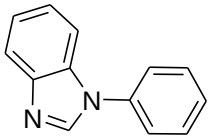


Following the general procedure 2-hydroxypyridine (100 mg, 1.05 mmol) was coupled with bromobenzene (0.11 ml, 1.07 mmol). The crude brown oil was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 144 mg (80 %) of the desired product **17** as a colourless solid.

MP: 126-127 °C. IR (KBr): 3049, 1657, 1599, 1579, 1525, 1491, 1452 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.30 (m, 7H), 6.70-6.64 (m, 1H), 6.28-6.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.43 (s), 140.95 (s), 139.90 (d), 138.01 (d), 129.34 (d), 128.50 (d), 126.54 (d),

121.88 (d), 105.96 (d) Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18; O, 9.35; Found: C, 77.21; H, 5.28; N, 8.23; O, 9.30.

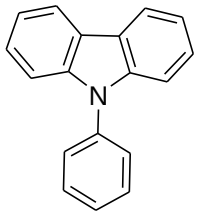
1-Phenyl-1H-benzo[d]imidazole (18)



Following the general procedure benzimidazole (100 mg, 0.92 mmol) was coupled with bromobenzene (0.10 ml, 0.94 mmol). The crude brown oil was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 144 mg (85 %) of the desired product **18** as solid.

MP: 94 °C. IR (KBr): 3056, 1595, 1500, 1452 $cm.^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.95-7.86 (m, 1H), 7.62-7.40 (m, 6H), 7.35-7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 141.9, 136.0, 133.2, 129.5, 127.8, 123.9, 123.5, 122.6, 120.4, 110.4. Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42; Found: C, 80.21; H, 5.29; N, 14.40. MS (ES) *m/z* (relative intensity) 195 ($[M+H]^+$ 100%).

9-Phenyl-9H-carbazole (19)



Following the general procedure carbazole (100 mg, 0.598 mmol) was coupled with bromobenzene (0.06 ml, 0.61 mmol). The crude brown oil was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 120 mg (82 %) of the desired product **19** as a colourless oil.

IR (neat): 3055, 1596, 1502, 1478, 1451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (m, 2H), 7.72-7.60 (m, 4H), 7.58-7.36 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.99 (s), 137.80 (s), 129.95 (d), 127.52 (d), 127.22 (d), 126.02 (d), 123.45 (s), 120.40 (d), 120.00 (d), 109.86 (d). Anal.Calcd.for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.76; Found: C, 89.01; H, 5.29; N, 5.56. MS (ES) *m/z* (relative intensity) 244 ($[M+H]^+$ 18%).

3.6. References

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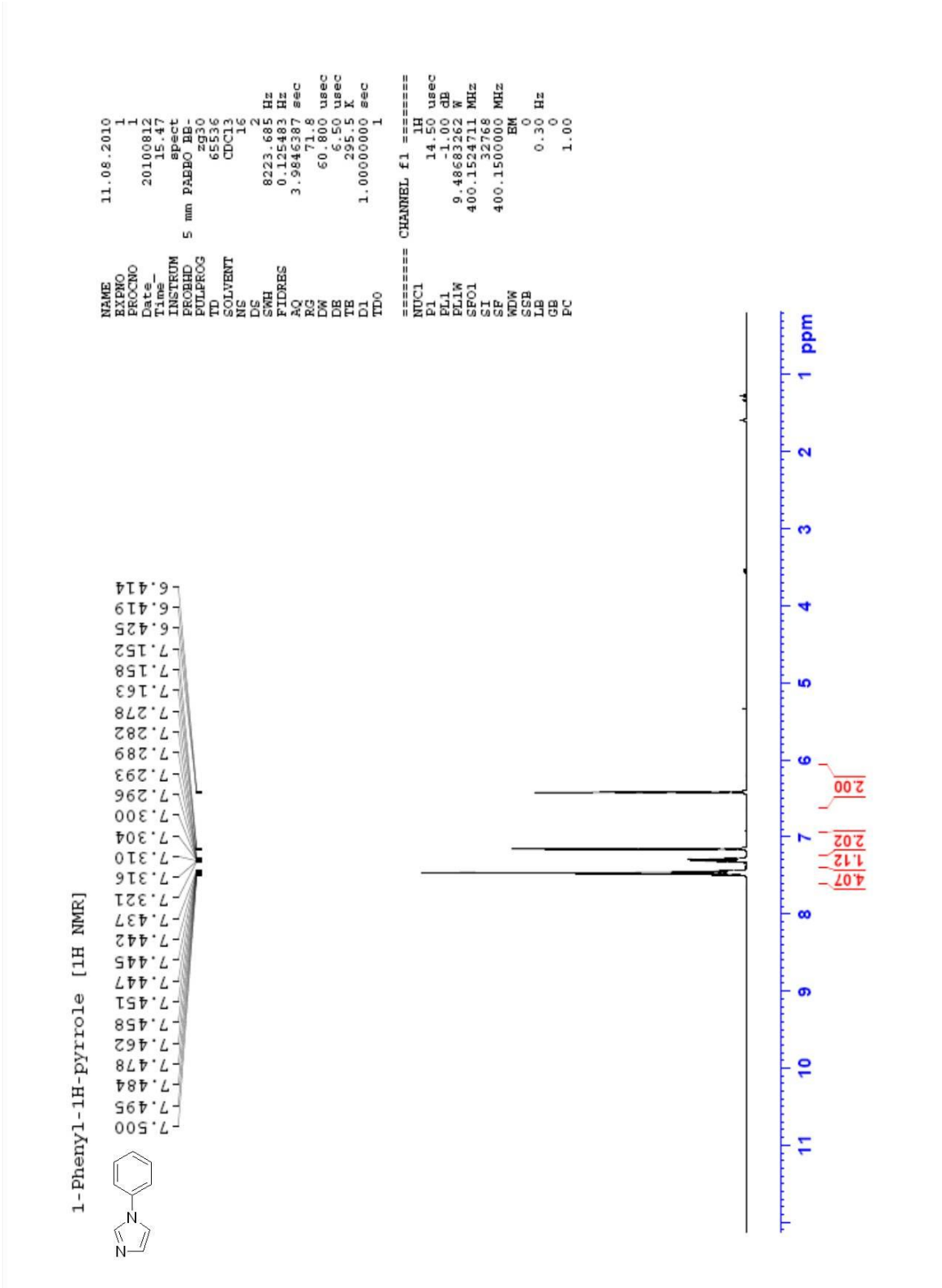
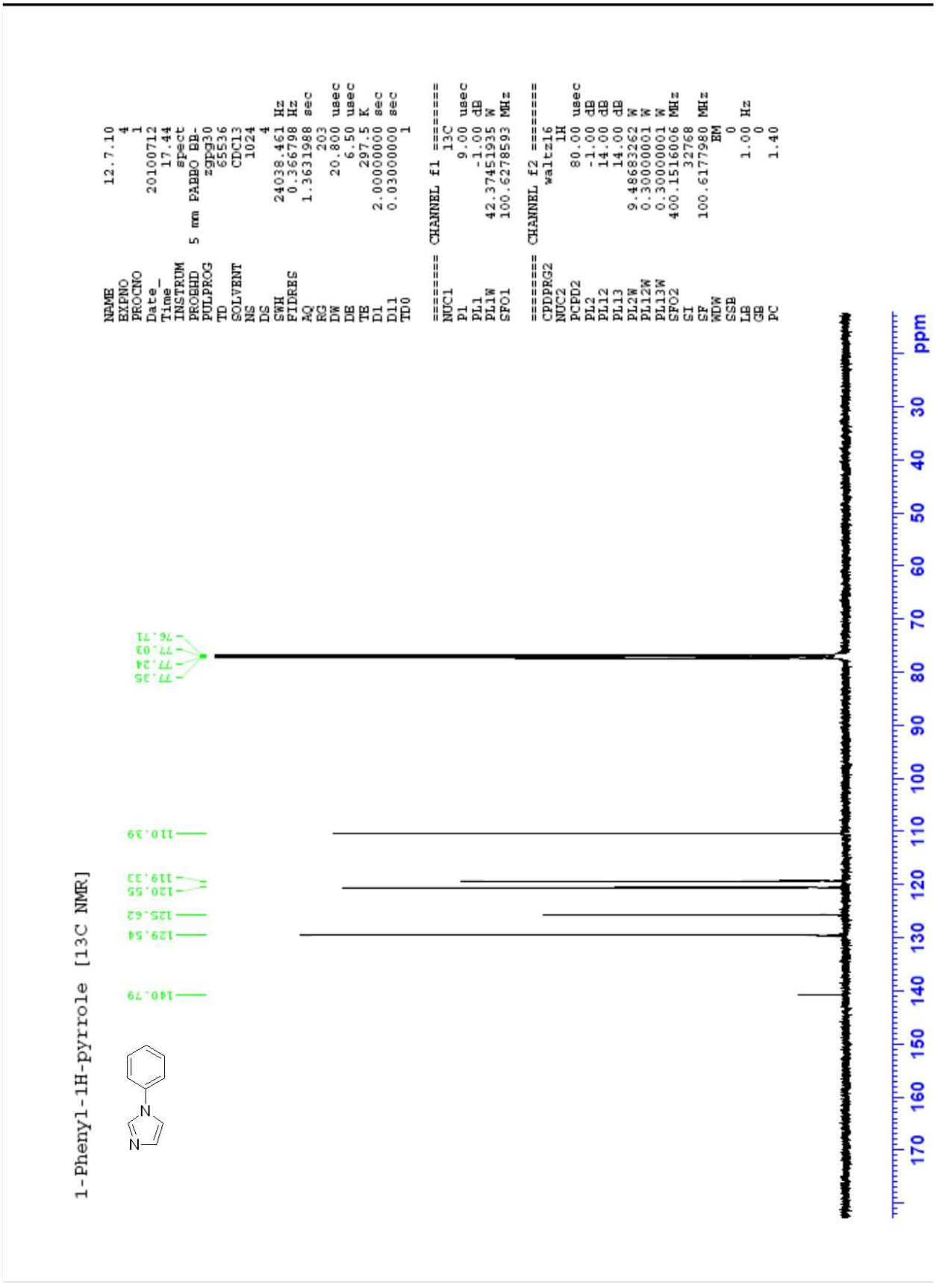
3.7. Selected NMR spectra

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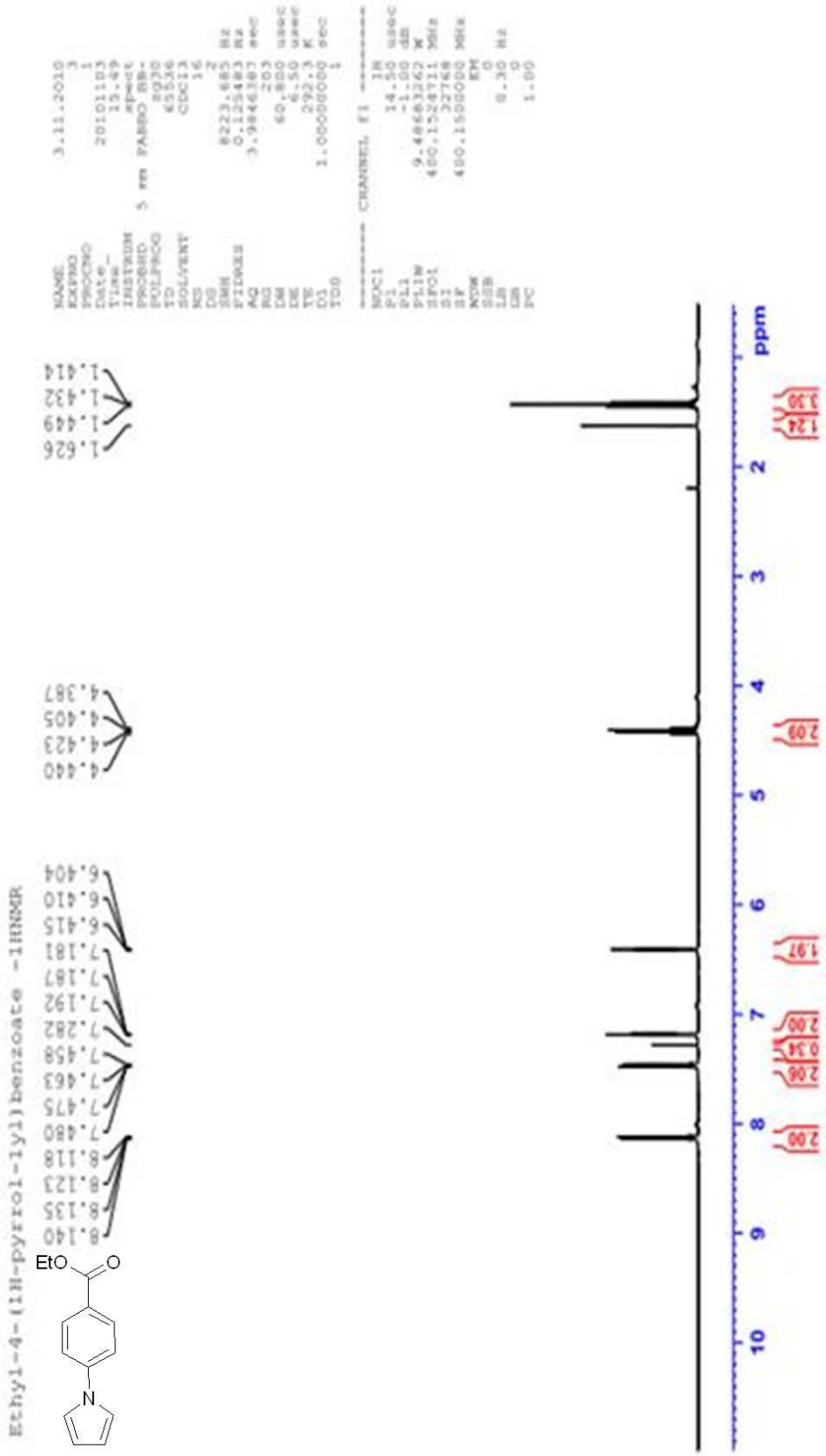
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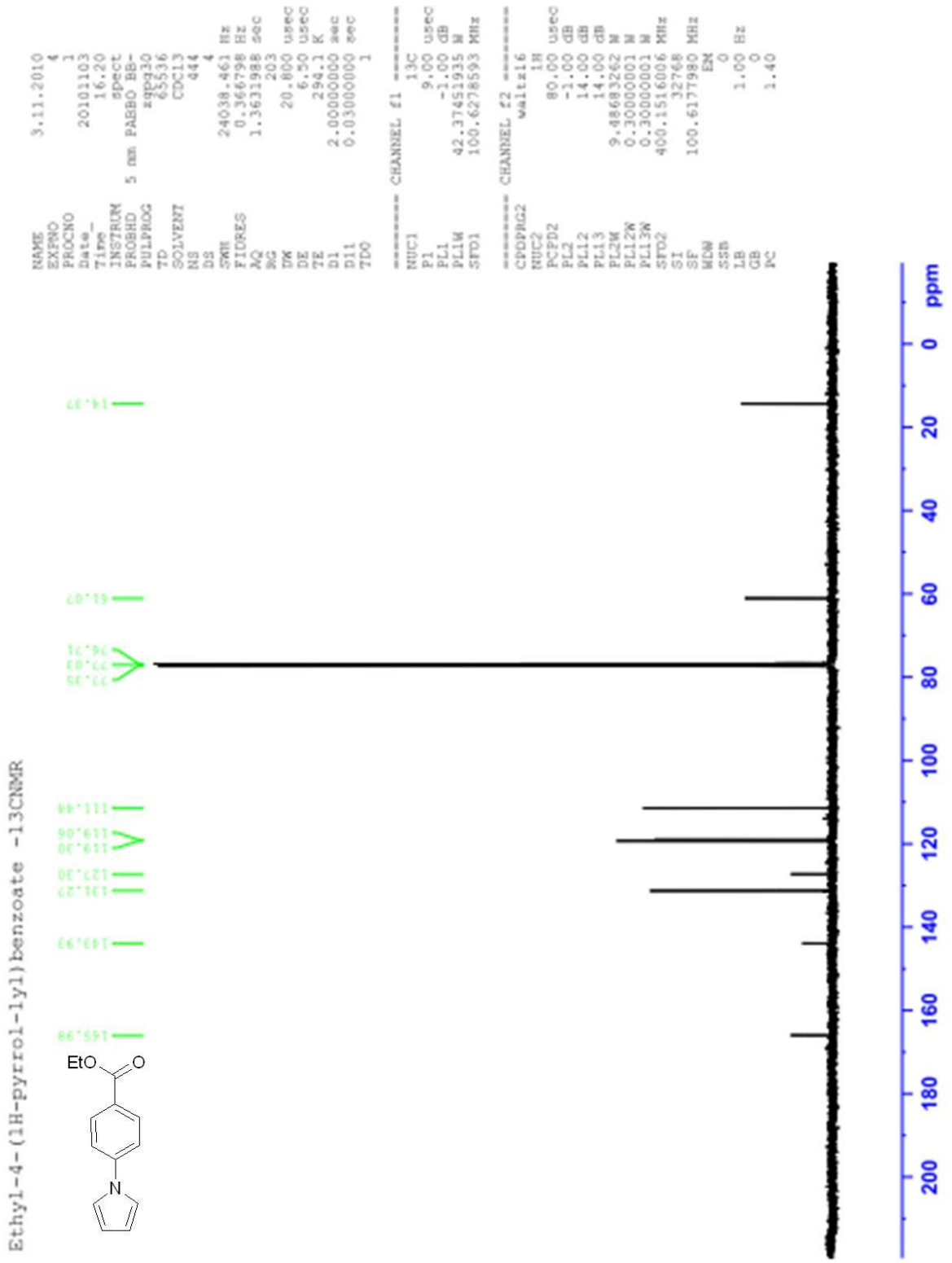
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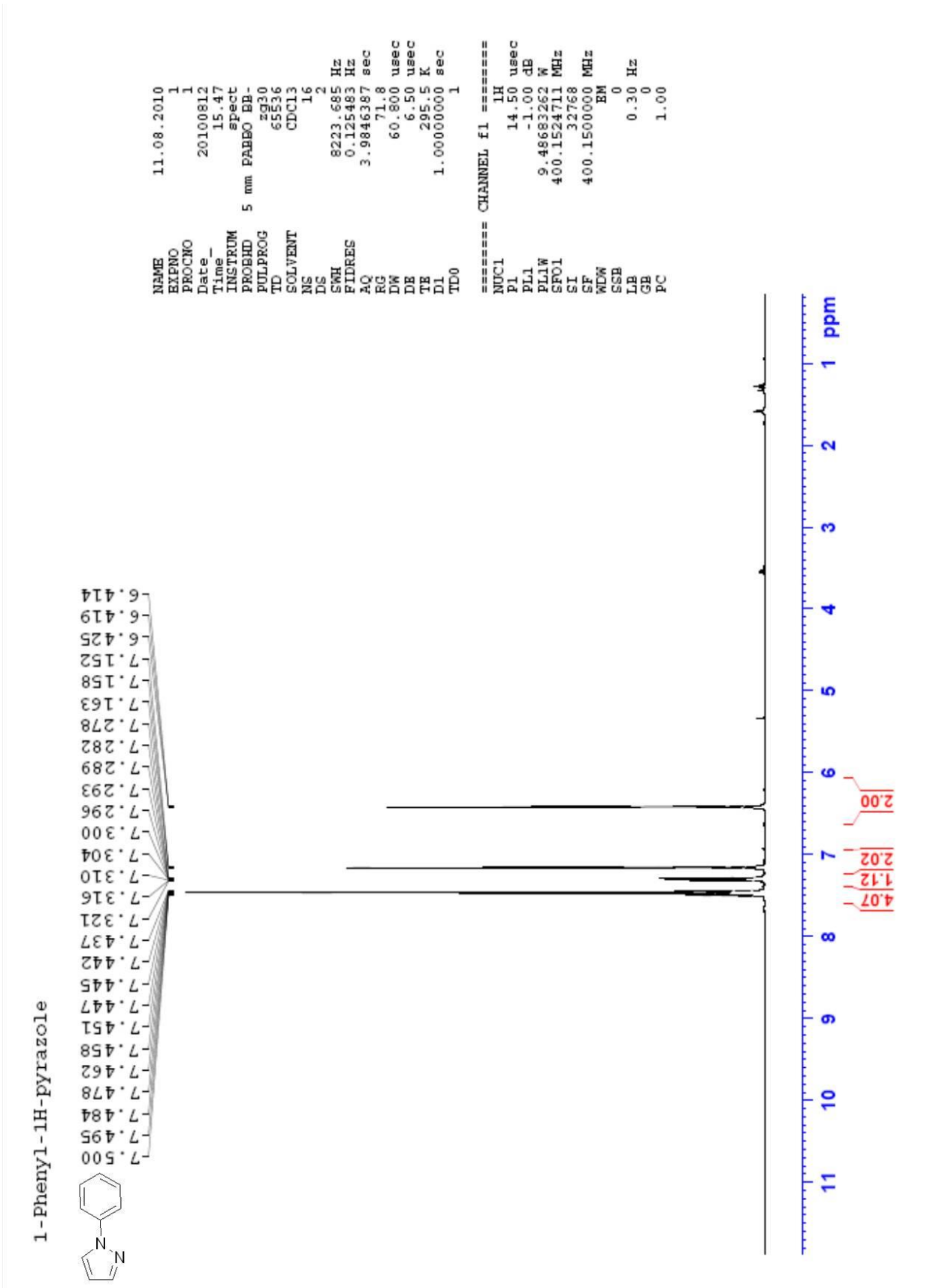
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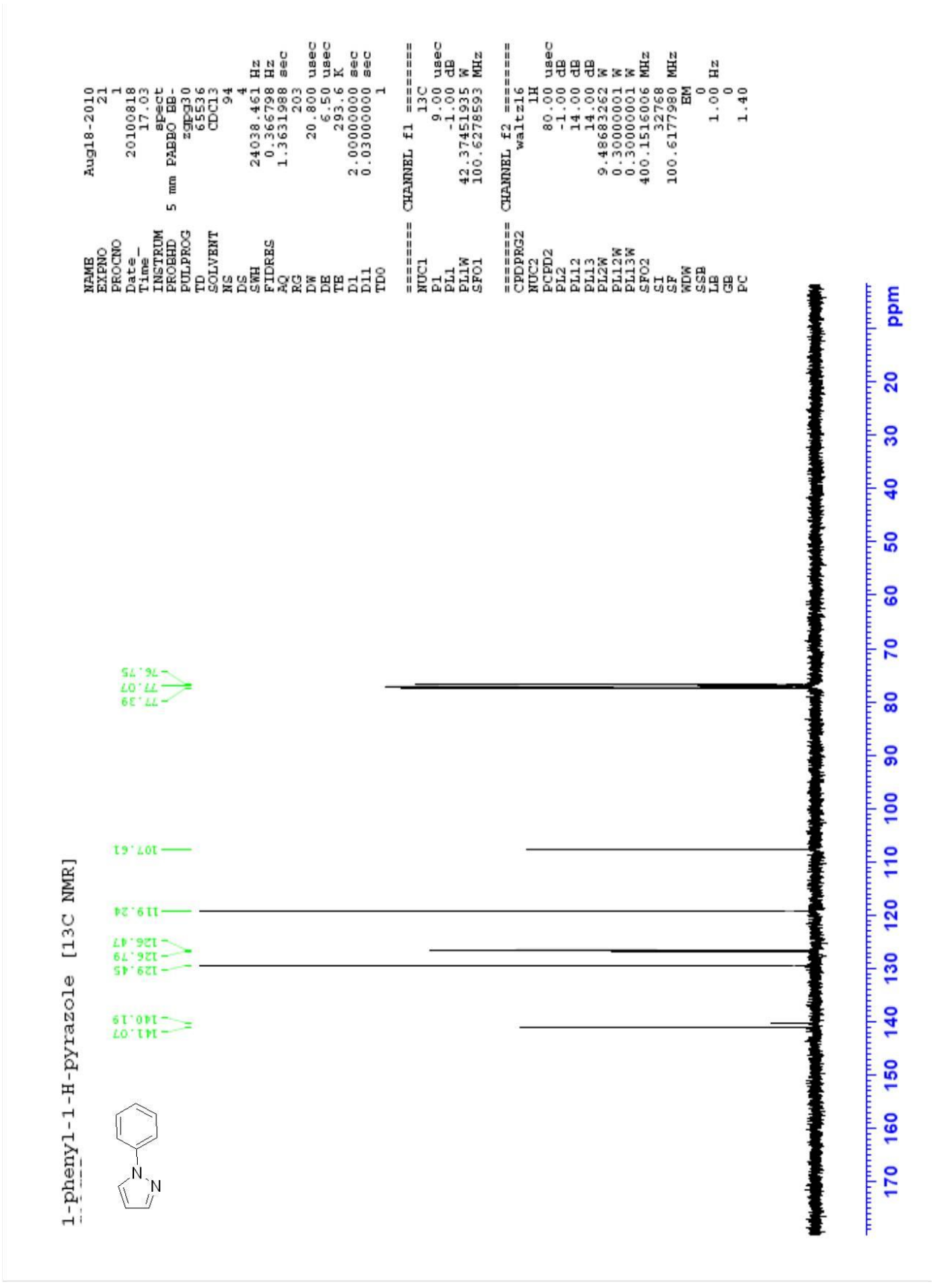
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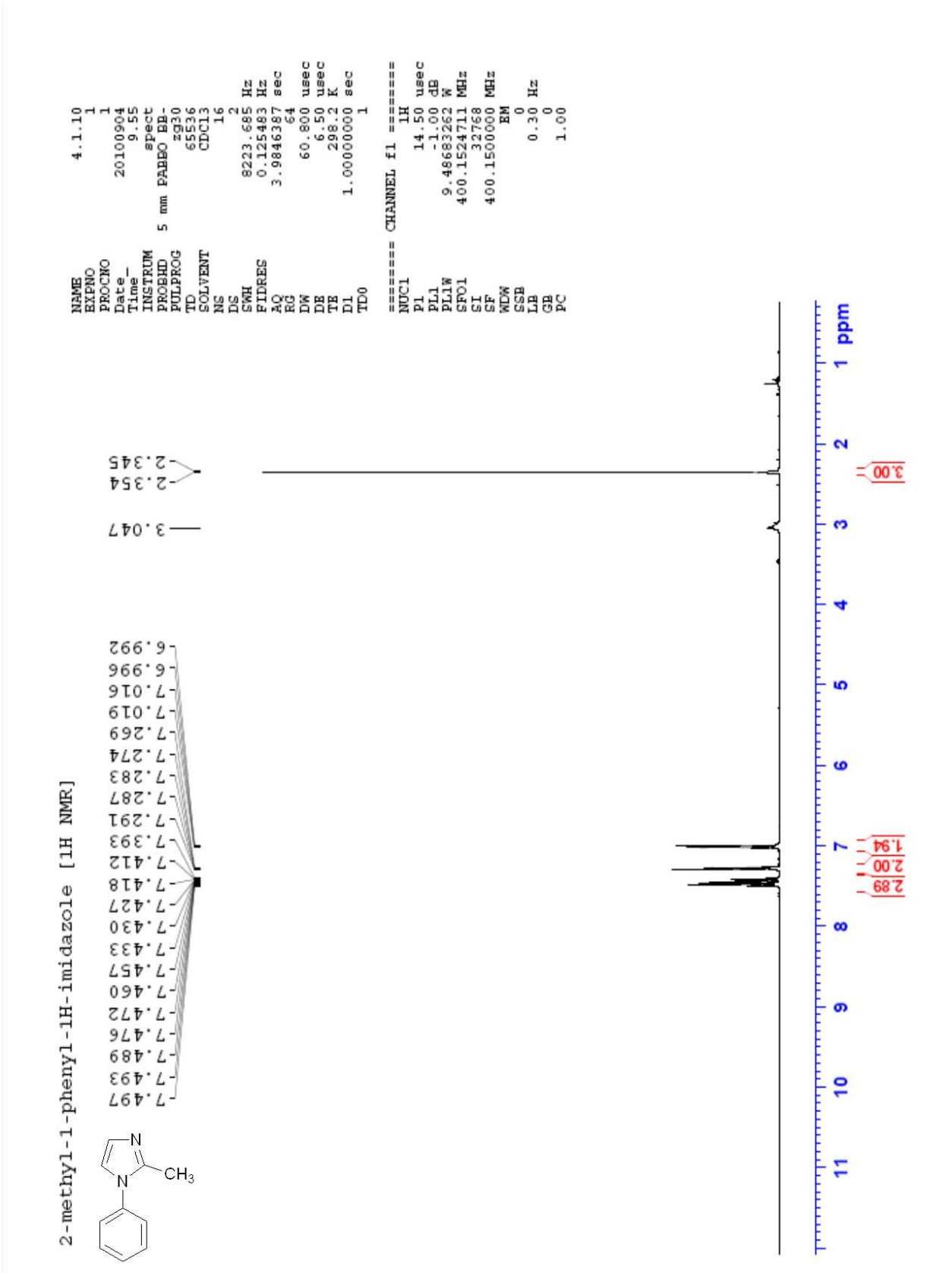
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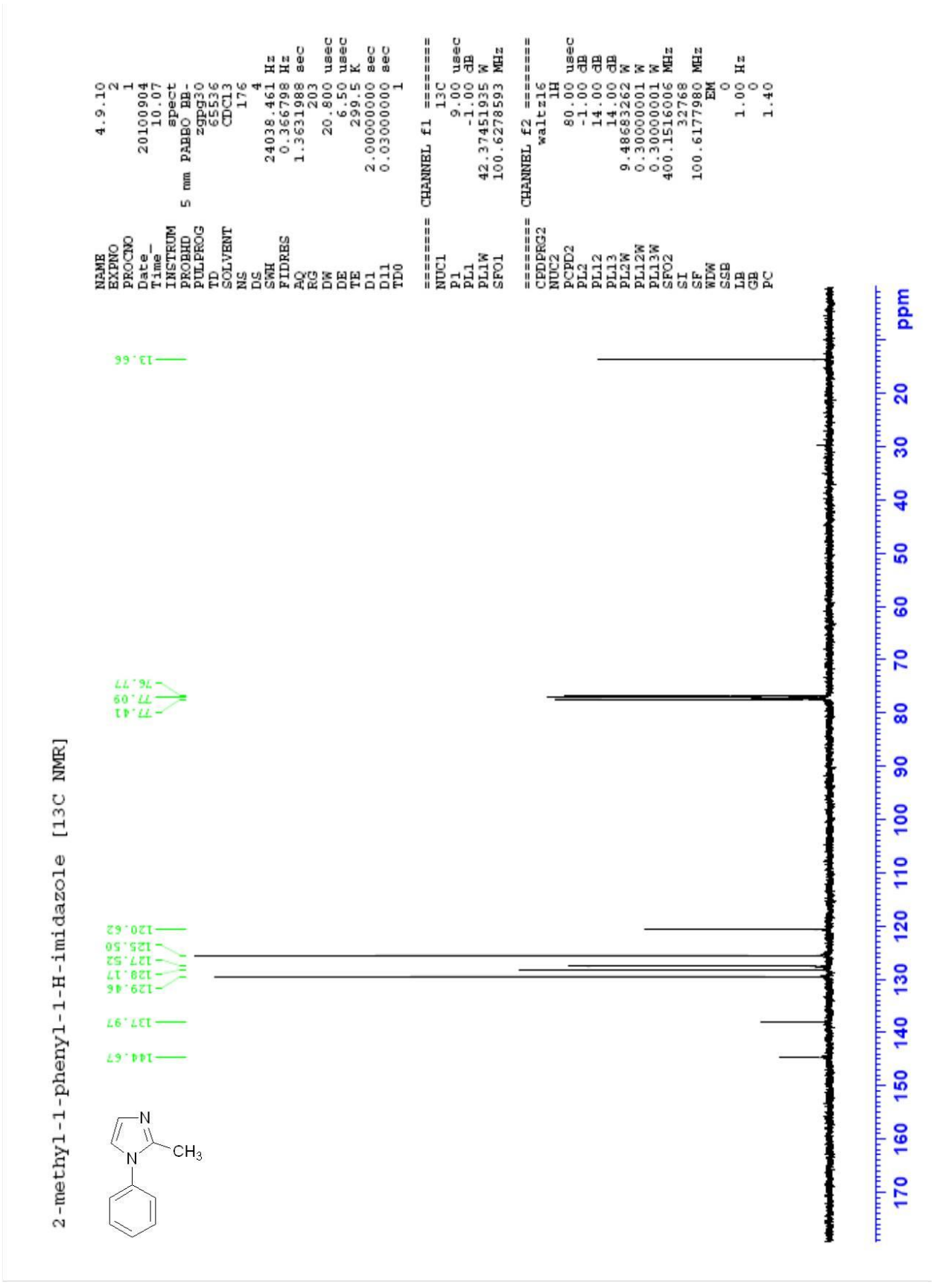
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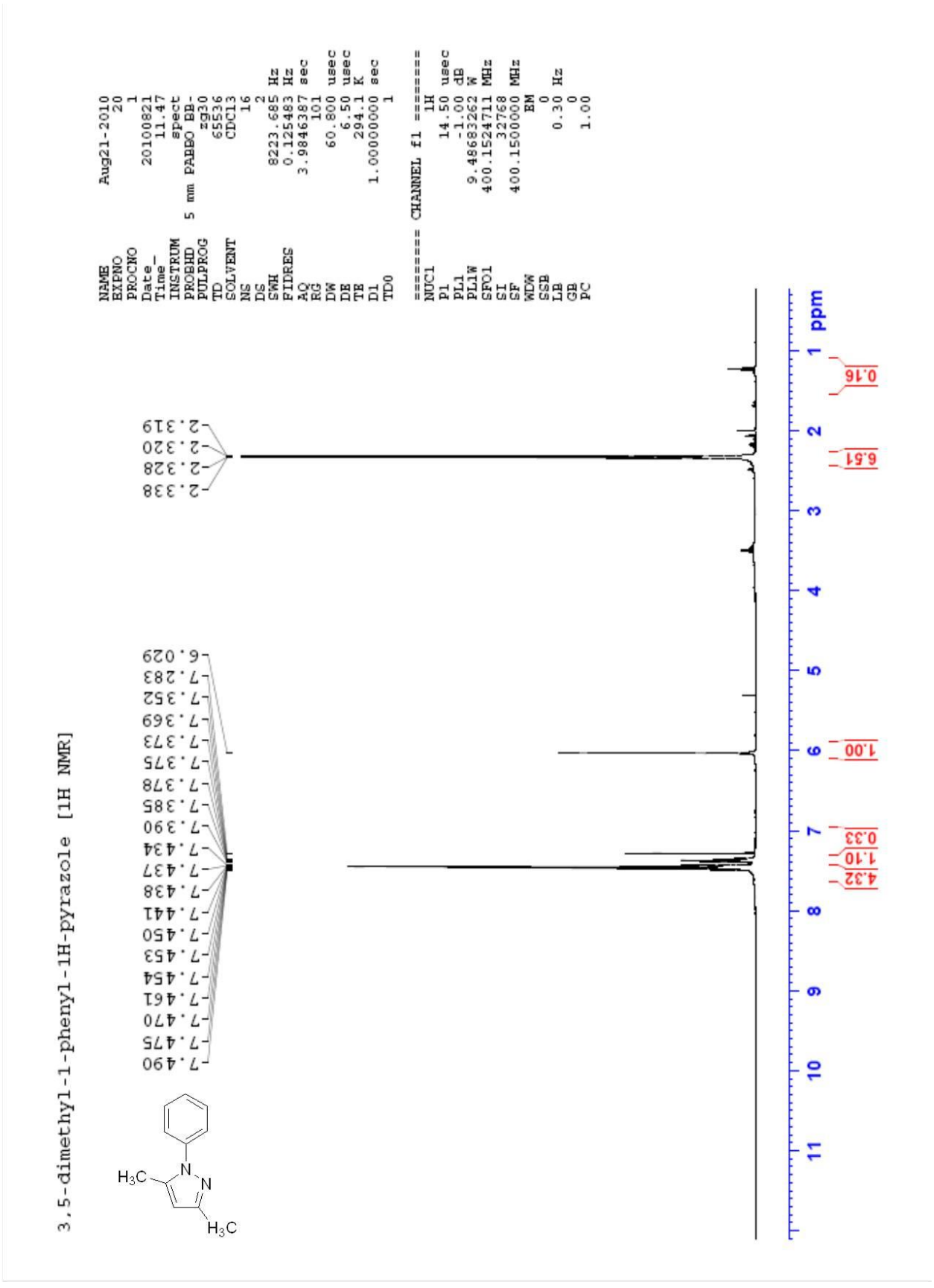
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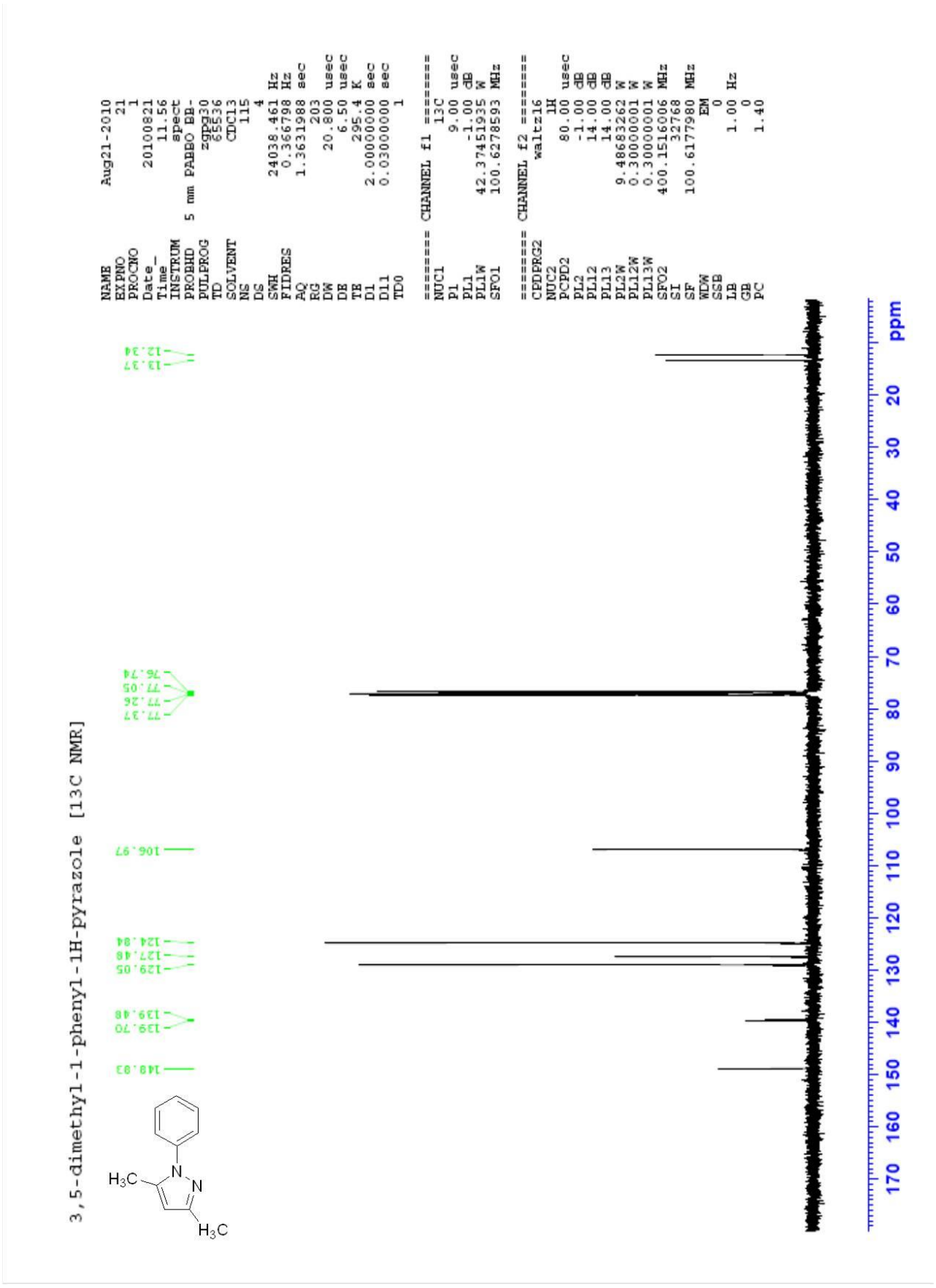
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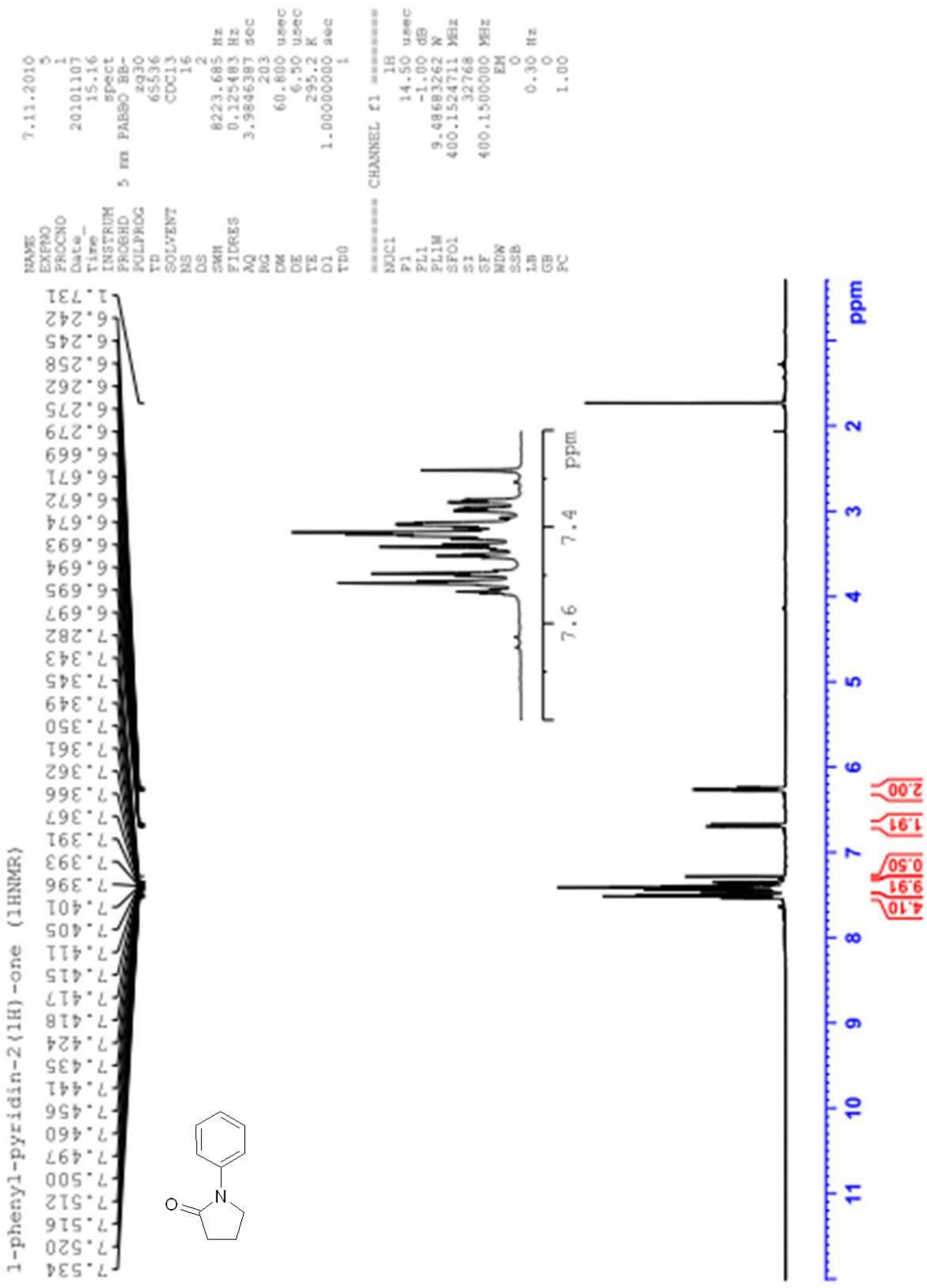
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PROCNO
Date_
Time
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AQ
RG
DW
DE
TE
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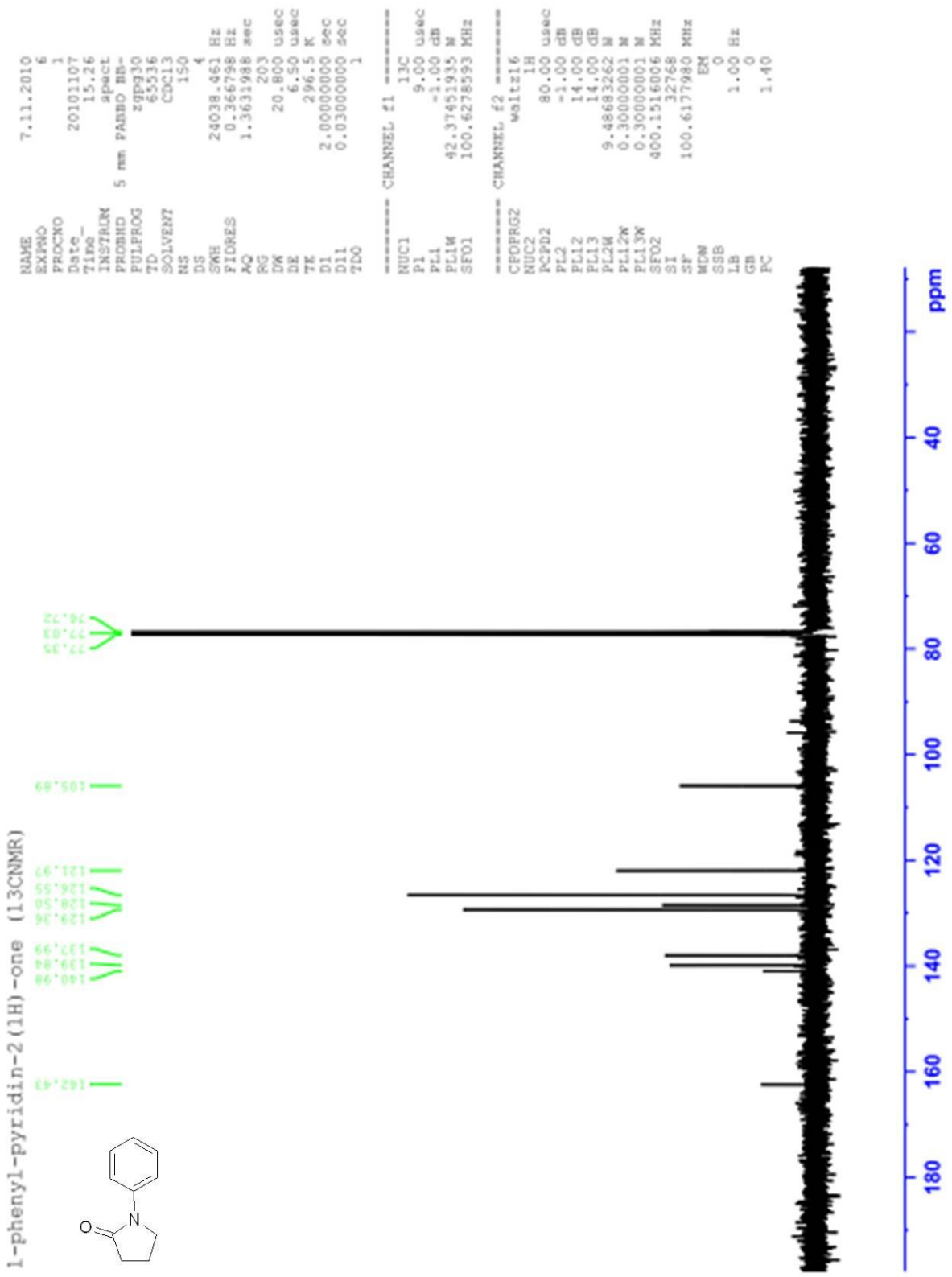
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Time 15.26
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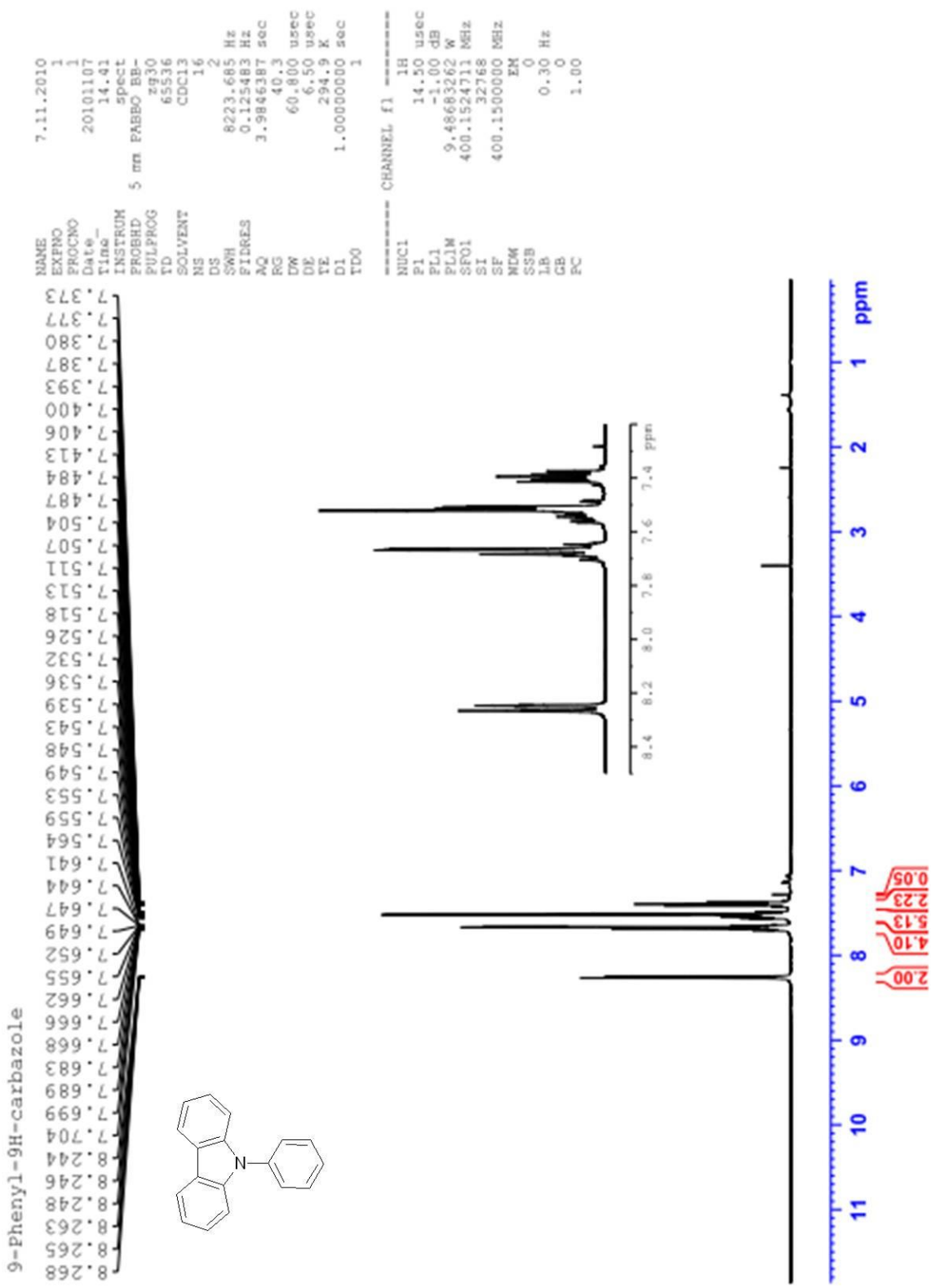
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PROCNO
Date_
Time
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FIDRES
AQ
RG
DW
DE
TE
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SF
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LB
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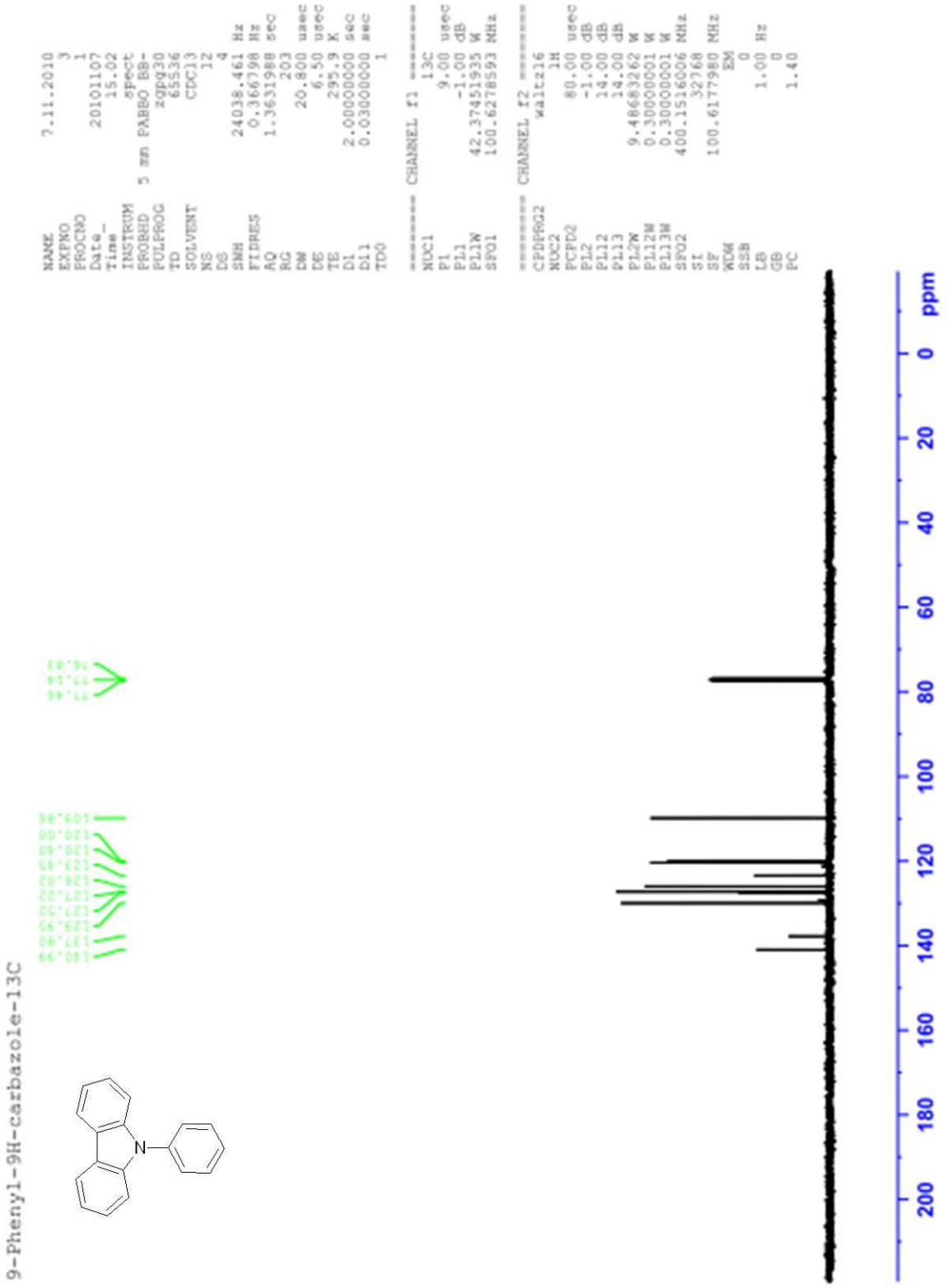
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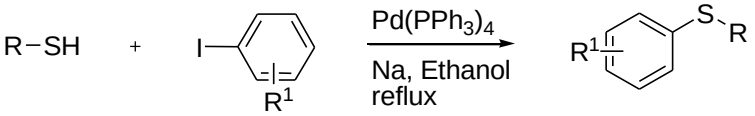
Chapter 4

$CuFe_2O_4$ catalyzed C-S cross-coupling reactions: Synthesis of dibenzothiazepines

4.1. Introduction

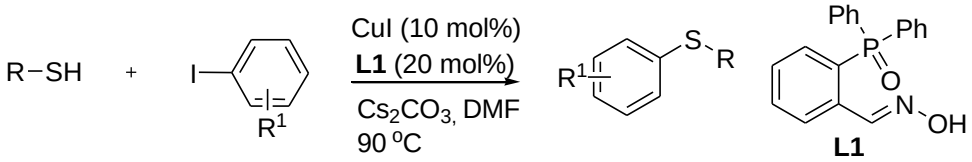
The formation of C(aryl)-S bond is of great importance because of the prevalence of these bond in many molecules that are of pharmaceutical and material interest.[1] For example, biaryl sulfides have been found as a common structural motifs in many drug candidates and have been used for the treatment of various diseases such as Alzheimer's and Parkinson's diseases,[2] human immunodeficiency virus diseases,[3] and cancer[4] etc. Traditionally, the C(aryl)-S bonds were synthesized under harsh reaction conditions such as elevated temperature (200 ^{o}C) in toxic, high boiling polar solvents like HMPA. Alternatively, these sulfides can be prepared by the reduction of aryl sulfones and sulfoxides using strong reducing agents like DIBAL-H or $LiAlH_4$.[5] To overcome these drawbacks, transition-metal catalysts are employed for various C-S bond forming reactions.[6] However, compared to N- and O-arylation reactions, S-arylation has been less studied due to the tendancy of thiols to undergo oxidative homocoupling S-S reactions. Also the organic sulfur compounds have a significant metal binding efficiency that leads to catalyst modification and/or deactivation.[7] In 1980, Migita and co-workers reported Pd-mediated C-S cross-coupling between thiols with aryl halides in refluxing ethanol (Scheme 1).[8]

Scheme 1



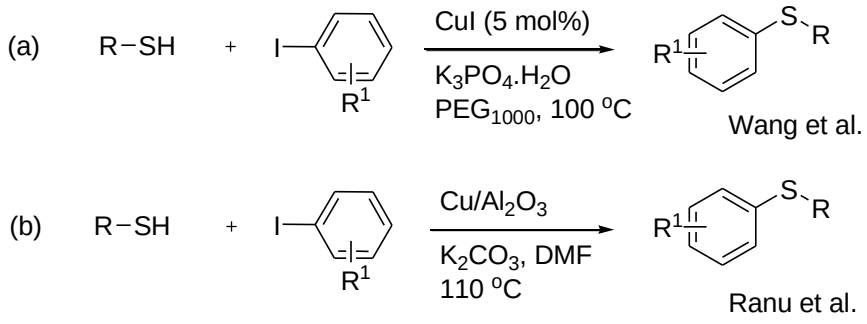
Subsequently, ligand-assisted Pd-catalyzed S-arylation reactions have been developed.[9] In spite of having wide scope and excellent compatibility with many functional groups, these protocols often suffer from the disadvantages resulting from the high cost and toxicity of the palladium precursors. Considering the cost and environmental factor, employment of Cu and Fe-based catalysts for such cross-coupling reactions is attractive one from industrial perspectives.[10] The group of Wan reported copper-catalyzed C-S cross-coupling of thiols with aryl iodides using oxime-phosphine oxide as the ligand in DMF (Scheme 2).[11] Besides copper catalyst, iron was found to be useful for the C-S cross-coupling reactions. Bolm et al. demonstrated an iron-mediated S-arylation of thiols with aryl iodides in toluene.[12]

Scheme 2



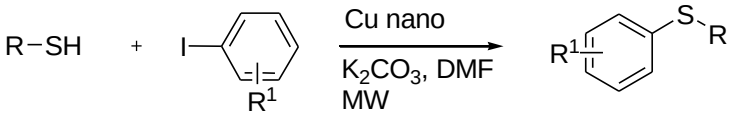
Furthermore, several ligands such as phosphazene, ethylene glycol, neocuproine, N-methylglycine, oxime-phosphine oxide ligand, tripod ligand, benzotriazole, 1,2-diaminocyclohexane, β-ketoester, L-proline, BINAM, polyethylene glycol, and ethylene diammine have been used as chelating agents in the copper- and iron-catalyzed cross-coupling reactions.[10] On the other hand, simple separation and regeneration of the catalyst from the reaction mixture are in strong demand for the cost-effective process of molecular synthesis. In pharmaceutical industries, it is also essential to remove all traces of metal residues, which frequently interfere with the subsequent reactions and contaminate the final products. In contrast, development of reusable heterogeneous catalytic systems for cross-coupling reactions have been received less attention although the situation is changing in recent years.[13] Evidently, certain heterogeneous catalytic systems for the S-arylation of thiols with aryl halides have been reported. For example, Wang and co-workers demonstrated ligand-free copper iodide catalyzed C-S cross-coupling of thiols with aryl iodides in PEG and PEG-H_2O. On recycling, the catalytic activity remain unaltered up to six cycles (Scheme 3a).[14] Similarly, heterogeneous copper catalyst supported on Al_2O_3 was employed for the selective S-arylations of thiols with iodobenzene in presence of K_2CO_3 and with bromobenzene in presence of Cs_2CO_3 in DMF at 110 °C (Scheme 3b).[15]

Scheme 3



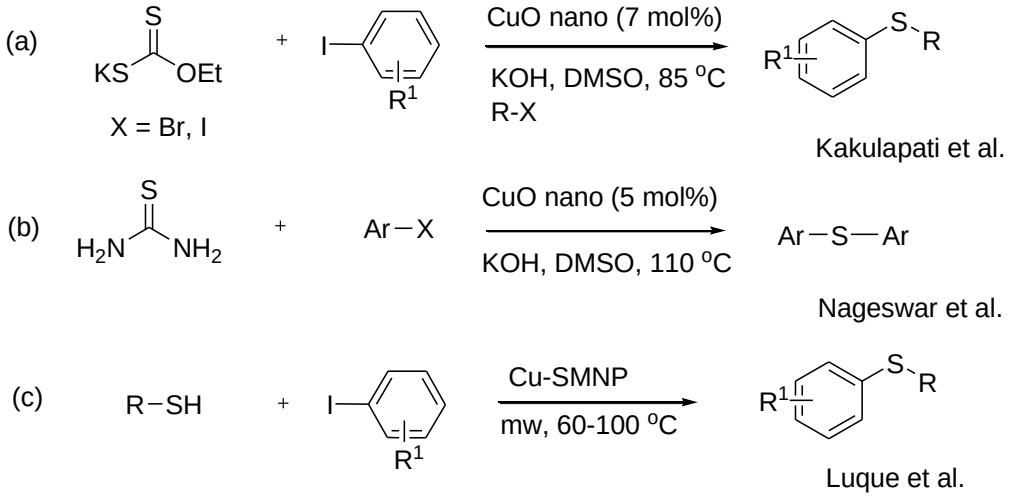
Recently, nanocatalyst receives significant attention due to its high surface area and low coordination sites. It also acts as a bridge between homogeneous and heterogeneous catalyst as it resembles the homogeneous catalyst with respect to high catalytic activity and selectivity and to heterogeneous catalyst with respect to recovery and reuse.[16] Ranu et al. reported microwave-assisted copper nanoparticles-catalyzed C-S cross-coupling between thiols with aryl iodides in DMF (Scheme 4).[17]

Scheme 4



Recently, CuO nanoparticles were used for the S-arylation reactions using ethyl potassium xanthogenate as the sulfur surrogates (Scheme 5a).[18] The CuO nanoparticles were further utilized for the synthesis of diarylsulfides using thiourea as the source of sulfur (Scheme 5b).[19] Luque et al. reported supported copper metal nanoparticles (Cu-SMNP) catalyzed S-arylation of thiols using microwave irradiation (Scheme 5c).[20]

Scheme 5



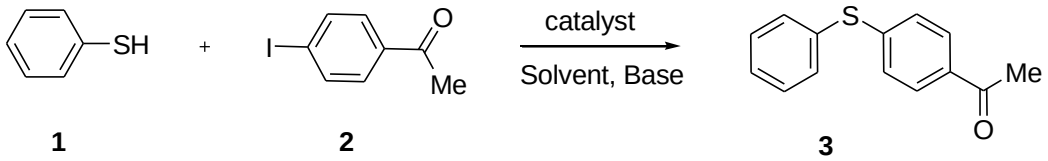
In continuation with our earlier work on $CuFe_2O_4$ nanoparticle-mediated C-N and C-C cross-coupling reactions,[21] here we extended the scope of similar catalytic system for C-S cross-coupling reactions. Subsequently, the catalytic activity of magnetic $CuFe_2O_4$ nanoparticles was also exploited for the one-pot synthesis of biologically important tricyclic dibenzothiazepines and their derivatives.

4.2. Results and Discussion

Recently, Mohapatra and her co-workers reported a thermal decomposition method for the synthesis of monodisperse, superparamagnetic ferrite nanoparticles.[22] In line with their work, we prepared superparamagnetic $CuFe_2O_4$ nanoparticles by thermal decomposition of $CuCl_2$ and $FeCl_3$ in ethylene glycol in presence of sodium acetate and ethanolamine. To evaluate the

efficiency of ferrite nanocatalysts in the C-S cross-coupling reactions, 4-iodoacetophenone **2** and thiophenol **1** was used as the model substrate for the optimization of the reaction conditions (Scheme 6) (Table 1).

Scheme 6



1 **2** **3**

Among the screened ferrite nanocatalysts, we observed that 10 mol % of $CuFe_2O_4$ nanoparticles afforded 95 % of 1-(4-(phenylthiophenyl)ethanone **3** using ^{t}BuOK as base in refluxing 1,4-dioxane. Other ferrite nanoparticles resulted low yield (5-15 %) of **3**. The presence of molecular ion peak at *m/*z 229 ($[M+H]^{+}$, $C_{14}H_{12}OS$) in MS (ES) and carbonyl absorption band at 1675 $cm.^{-1}$ in IR spectrum suggest the formation of **3.** The ^{1}H and ^{13}C NMR of **3** also agreed with the structure. It may be mentioned here that copper ferrite nanoparticles (10-25 nm) prepared by our earlier co-precipitation method[22] also provide S-arylated product with almost similar yield (entry 1). It was also observed that when the coupling reaction was carried out in open air or in oxygen atmosphere, low yield of **3** was obtained (Table 1, entries 18, 19). The decrease in yield may be due to the oxidative homocoupling of thiophenols.

The influence of base towards the coupling reactions was examined by conducting a series of experiments using $CuFe_2O_4$ nanoparticles as catalyst in refluxing 1,4-dioxane. When the reaction was carried out using Cs_2CO_3 as the base, only 30 % of the coupling product **3** was isolated. Other bases like K_2CO_3, NaOAc, $NaHCO_3$ and Et_3N did not improve the product yield. Changing the carbonate base to ^{t}BuOK, we observed complete consumption of the starting materials and the product **3** was obtained in 95 % yield.

The influence of solvent was tested by conducting the reactions in a range of solvents. Among the screened solvents, 1,4-dioxane proved to be superior as compared to other solvents. Solvents like MeOH, toluene and acetonitrile were found to be ineffective where as DMSO resulted only 40 % of the product. On refluxing the reactions in DMF, 90 % of the **3** was obtained. Further increase in yield of the reaction was noticed by refluxing the reaction mixture in 1,4-dioxane solvent.

Table 1. C-S cross-coupling between thiophenol with 4-iodoacetophenone in different solvents and bases in presence of ferrite nanoparticles.

Entry	Catalyst	Solvent	Base	Yield (%)
1	$CuFe_2O_4$	DMF	^tBuOK	90
2	$CuFe_2O_4$	1,4-dioxane	^tBuOK	95
3	$CuFe_2O_4$	MeOH	^tBuOK	08
4	$CuFe_2O_4$	Toluene	^tBuOK	24
5	$CuFe_2O_4$	CH_3CN	^tBuOK	18
6	$CuFe_2O_4$	DMSO	^tBuOK	48
7	$CuFe_2O_4$	1,4-dioxane	Cs_2CO_3	30
8	$CuFe_2O_4$	1,4-dioxane	K_2CO_3	20
9	$CuFe_2O_4$	1,4-dioxane	NaOAc	≤5
10	$CuFe_2O_4$	1,4-dioxane	$NaHCO_3$	10
11	$CuFe_2O_4$	1,4-dioxane	Et_3N	18
12	Fe_3O_4	1,4-dioxane	^tBuOK	≤5
13	$CoFe_2O_4$	1,4-dioxane	^tBuOK	10
14	$NiFe_2O_4$	1,4-dioxane	^tBuOK	15
15	CuO	1,4-dioxane	^tBuOK	59
16	$CuFe_2O_4$		^tBuOK	00
17		1,4-dioxane	^tBuOK	00
18	$CuFe_2O_4$	1,4-dioxane	^tBuOK	39
19	$CuFe_2O_4$	1,4-dioxane	^tBuOK	25

Reaction conditions: 0.90 mmol of thiophenol, 1.80 mmol of 4-iodoacetophenone, 10 mol % of catalyst, 2.0 equiv of base, 5 mL of solvent, 24 h reflux under N_2 atmosphere.

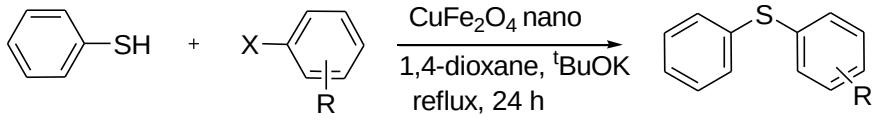
The optimized condition for C-S cross coupling reaction involves the utilization of 10 mol % $CuFe_2O_4$ as the catalyst and 2 equiv of ^tBuOK as the base in 1,4-dioxane solvent.

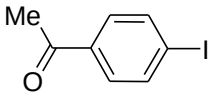
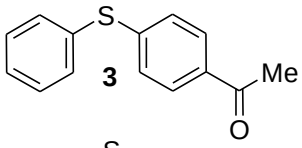
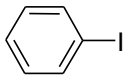
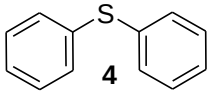
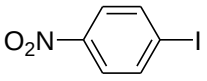
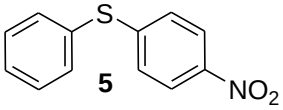
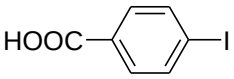
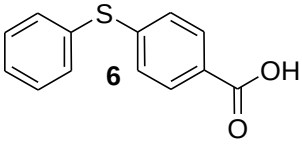
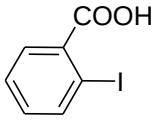
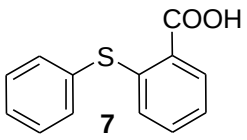
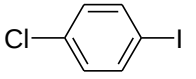
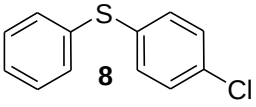
Substrate Scope

With the optimized reaction conditions, we then investigated the scope of this catalytic protocol for the cross-coupling of a diverse range of halides with thiophenol. As shown in the

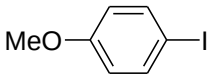
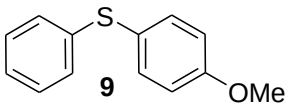
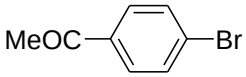
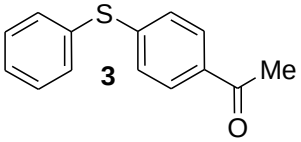
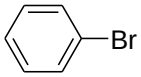
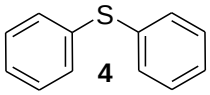
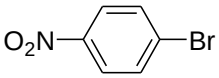
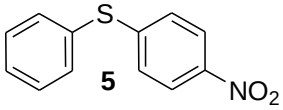
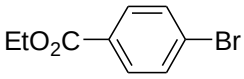
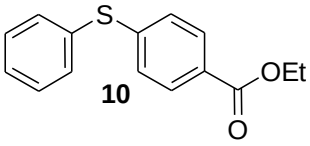
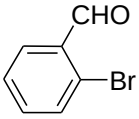
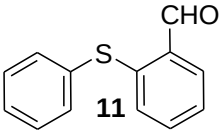
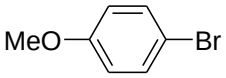
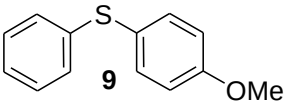
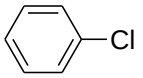
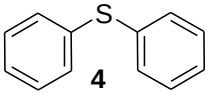
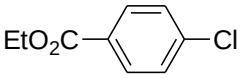
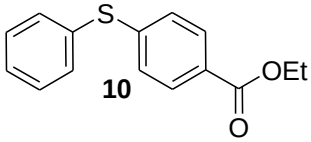
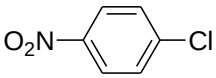
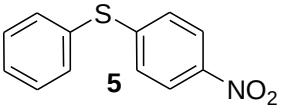
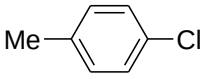
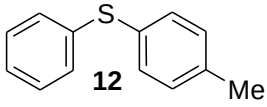
Table 2, the coupling of thiophenol with aryl iodides was successful, leading to the desired products in good to excellent yield and we did not observe any trace of homocoupling product (e.g. diphenyl disulfides) from TLC. In case of coupling of thiophenol with 4-nitroiodobenzene, a slight decrease in yield was obtained (Table 2, entry 3). This may be due to the possible decomposition of the 4-nitroiodobenzene. When the cross-coupling between thiophenol and 4-iodochlorobenzene was carried out, good chemoselectivity was observed resulting **8** in good yield. Notably, the sterically congested 2-iodobenzoic acid afforded 90 % of the S-arylated product (Table 2, entry 4).

Table 2. $CuFe_2O_4$ catalyzed C-S cross-coupling of thiophenol with aryl halides



Entry	Aryl halide	Product	Yield (%)
1		 **3**	95
2		 **4**	98
3		 **5**	86
4		 **6**	87
5		 **7**	90
6		 **8**	88

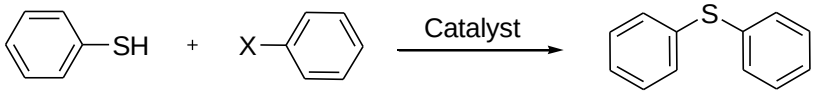
Continued..

Entry	Aryl halide	Product	Yield (%)
7		 **9**	83
8		 **3**	87
9		 **4**	85
10		 **5**	62
11		 **10**	76
12		 **11**	72
13		 **9**	62
14		 **4**	48
15		 **10**	45
16		 **5**	42
17		 **12**	47

Reaction conditions: 0.90 mmol of thiophenol, 1.80 mmol of halide, 10 mol % of catalyst, 2.0 equiv of ^{t}BuOK, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

Next we studied the scope of the reactions of thiophenol with different aryl bromides having both electron-donating and -withdrawing groups (Table 2, entries 8-13). Good yield of the S-arylated product was obtained in case of 4-bromoacetophenone (87 %), bromobenzene (85 %), 2-bromobenzaldehyde (72 %) and 4-bromoethylbenzoate (72 %). Moderate yield in case of 4-nitrobromobenzene and 2-bromobenzaldehyde is accounted for their possible decomposition, where as 4-bromoanisole resulted competitive homocoupled diphenyl disulfide (14 %). More interestingly, our catalytic system was also applicable towards less reactive aryl chlorides. The reactions of thiophenol with chlorobenzene, 4-chloroethylbenzoate and 4-nitrochlorobenzene resulted 48, 45, and 42 % desired product respectively along with a reasonable amount of diphenyl disulfide (17-25 %) (Table 2, entries 14-17). Notably, the earlier copper-mediated C-S coupling reactiions resulted very poor yield of the S-arylated product with aryl bromides and aryl chlorides.[23, 20] Similarly, Bolm's iron-mediated coupling methodology did not afford any S-arylated product with aryl bromides and aryl chlorides.[12] Although Saker's copper mediated methodology afforded S-arylated product with aryl bromides but found ineffective toward aryl chlorides (Table 3).[23e]

Table 3. Comparision study on cross-coupling of C_6H_5Br and C_6H_5Cl with PhSH in presence of different catalysts



Catalyst	Aryl halide	Yield (%)	References
$FeCl_3$/DMEDA	X = I	91	Bolm et al.[12]
	X = Cl, X = Br	00	
CuO nano	X = I	95	Punniyamurthy et al.[23b]
	X = Br	37	
	X = Cl	< 5	

Continued..

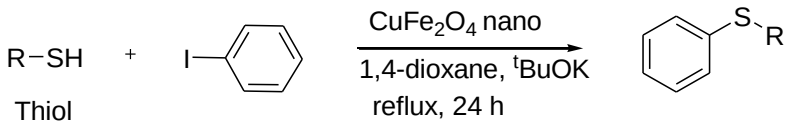
Catalyst	Aryl halide	Yield (%)	References
Cu-MW-HMS	X = I	95	Luque et al.[20]
	X = Br	nd	
	X = Cl	nd	
Cu/NMP	X = I	99	van Koten et al.[23c]
	X = Br	5	
	X = Cl	4	
Cu/L/MW	X = I	86	Bagley et al.[23d]
	X = Br	32	
	X = Cl	00	
$Cu(OTf)_2$/BINAM	X = I	97	Sekar et al.[23e]
	X = Br	66	
	X = Cl	00	
CuI nano/nBu_4NOH	X = I	93	Xu et al.[23f]
	X = Br	61	
	X = Cl	Trace	

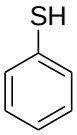
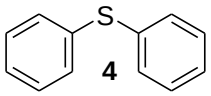
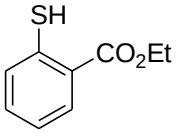
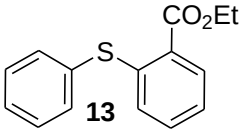
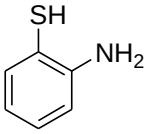
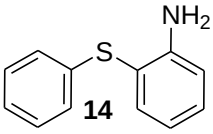
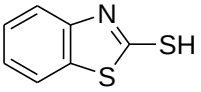
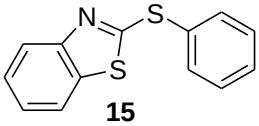
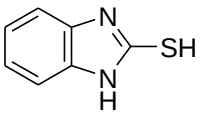
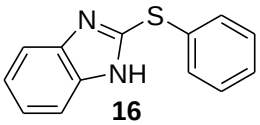
Thus our catalytic system show good tolerance to both electron-withdrawing and -donating functional groups and also to the presence of functional groups at ortho-position of the aryl iodides and bromides.

Having the proved cross-coupling efficiency of our catalytic protocol with aryl halides, the scope of the reaction was subsequently extended to a range of aryl and alkyl thiols. Aryl thiols having both electron-donating and -withdrawing groups undergo the C-S cross-coupling reactions with iodobenzene to afford the corresponding product in 60-85 % yield (Table 4, entries 2, 9, 10, 11). The coupling reaction showed good chemoselectivity as evidenced by the

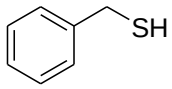
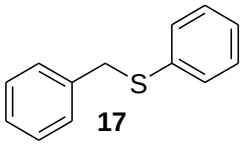
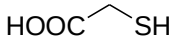
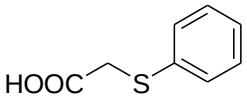
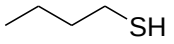
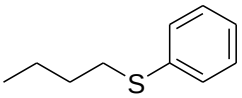
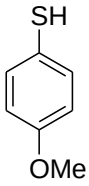
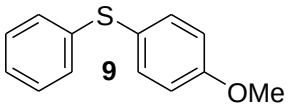
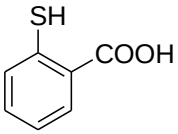
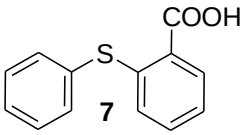
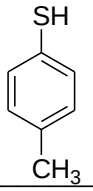
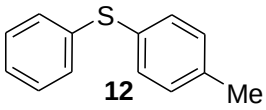
formation of S-arylated product in presence of free amino group (Table 4, entry 3).Then we investigated the C-S cross-coupling reactions toward the benzofused heteroarylthiols. The coupling of benzo[*d*]thiazole-2-thiol and 1H-benz[*d*]imidazole-2-thiol with iodobenzene resulted the product **15** and **16** in 88 % and 82 % respectively. Interestingly, good chemoselectivity was observed in case of benzo[*d*]thiazole-2-thiol, affording only S-arylated product (Table 4, entry 5). This may be due to the increased nucleophilicity of the thiol. Alkane thiols were also found to be effective nucleophiles for these reactions (Table 4, entries 6-8). Butanethiols and benzyl mercaptan coupled with the iodobenzene affording the cross-coupled product in good yield. But in case of 2-mercaptoacetic acid a low yield of 40 % was obtained.

Table 4. $CuFe_2O_4$ catalyzed C-S cross-coupling of thiols with iodobenzene



Entry	Thiol	Product	Yield (%)
1		 **4**	98
2		 **13**	78
3		 **14**	85
4		 **15**	82
5		 **16**	88

Continued..

Entry	Thiol	Product	Yield (%)
6		 **17**	86
7		 **18**	40
8		 **19**	80
9		 **9**	60
10		 **7**	60
11		 **12**	80

Reaction conditions: 0.90 mmol of thiol, 1.80 mmol of iodobenzene, 10 mol % of $CuFe_2O_4$, 2.0 equiv of ^tBuOK, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

Tandem C-S/C-N bond formations: Synthesis of dibenzothiazepine derivatives

Next, we deem for the one-pot synthesis of diaryl-fused thiazepine derivatives by the tandem C-S and C-N bond forming reactions. It is worthy to mention that dibenzo-fused thiazepines having medium-ring (6-7-6) structures show pronounced therapeutic effect on the central nervous system and are particularly active as antidepressants, antimetics, analgesiscs and sedatives.[24-25] Successful examples include dibenzothiazepine drugs (e.g. Quetiapine and Clothiapine), which are clinically used for the treatment of bipolar and psychiatric disorders (Fig.1).

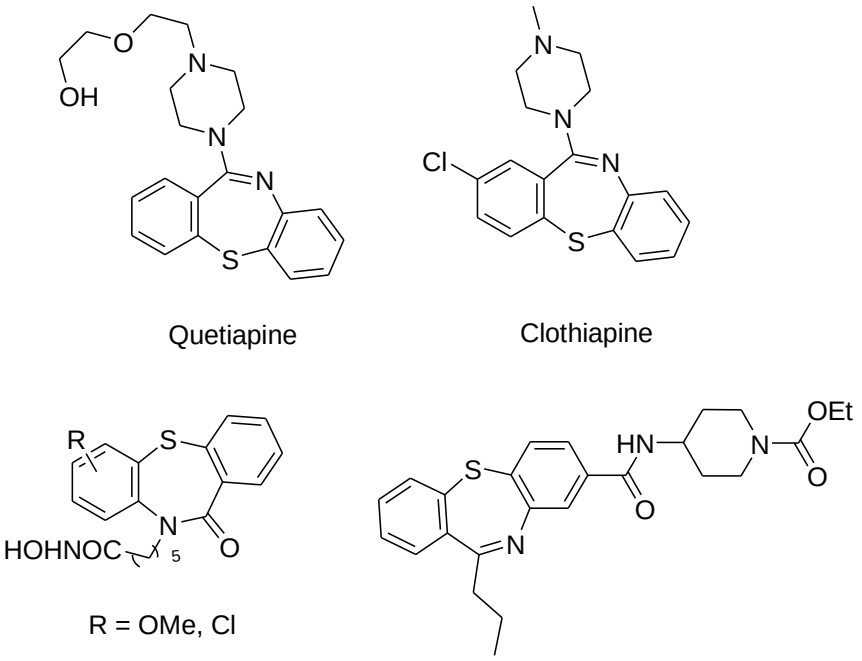
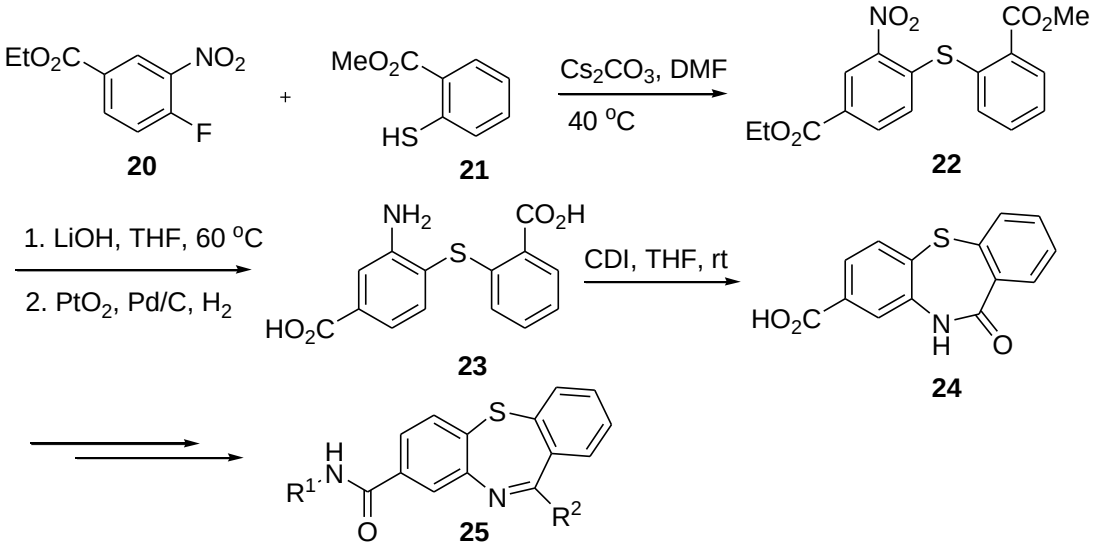


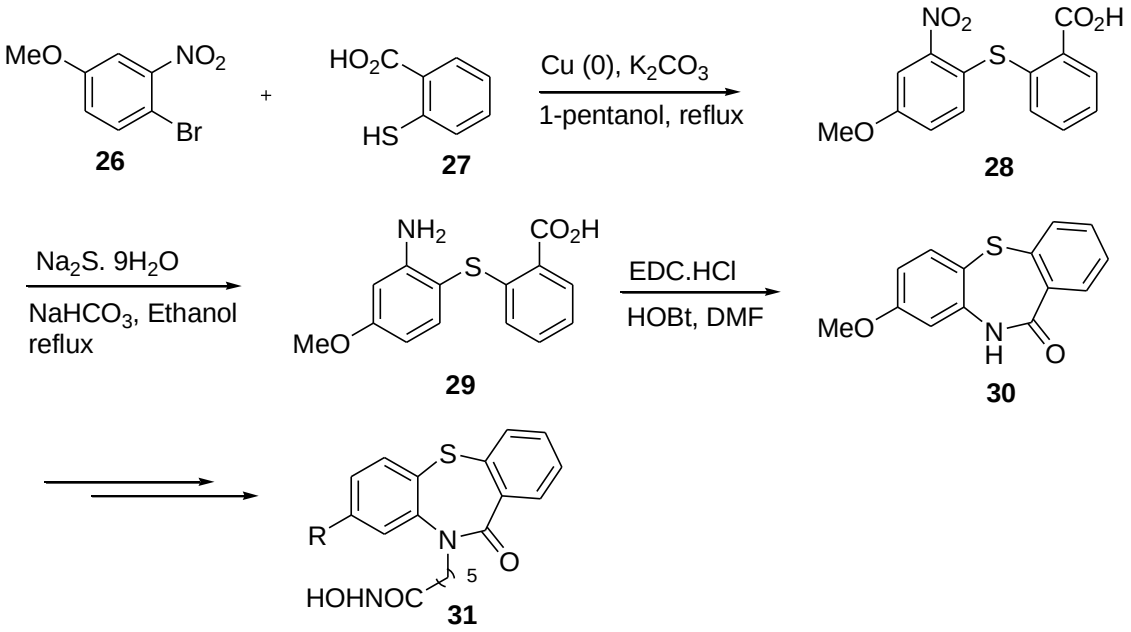
Fig. 1. Some biologically potent dibenzo-fused thiazepines

Recently, Garattini and co-workers prepared the dibenzothiazepine-11-one derivatives **24** by coupling the thio ester **21** with aryl fluorides **20** and described the anti-tumor potential of the synthesized compounds **25** in animals (Scheme 6).[26] Petterssons and co-workers also followed a similar type of multistep methodology for the synthesis of **30** and described the CBI inverse agonist behavior of dibenzothiazepine derivative **31** (Scheme 7).[27]

Scheme 6

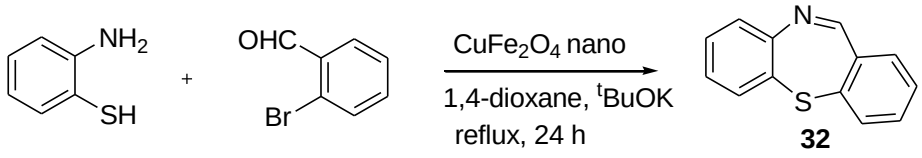


Scheme 7



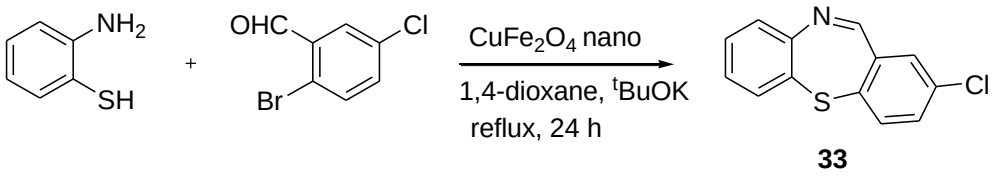
However, requirement of strongly electron-withdrawing groups and multistep procedure towards the synthesis of dibenzothiazepinone nucleous reduce the attractiveness of these methodologies. But the emerging pharmacological potential of dibenzothiazepine ring systems makes them a valuable target and hence, short and efficient routes for their synthesis are desired. In this regard, we thought that if we coupled the 2-aminothiophenol with 2-bromobenzaldehyde, the dibenzo-fused thiazepines could be resulted (Scheme 8). Interestingly, employing our optimized reaction conditions (10 mol % $CuFe_2O_4$ nanoparticles, 2 equiv ^tBuOK, 1,4-dioxane) for the coupling between 2-aminothiophenol and 2-bromobenzaldehyde, we were getting 65 % of the dibenzothiazepines **32**.

Scheme 8



Encouraged by these results we tried to synthesize substituted dibenzothiazepine derivatives. Thus, when 4-chloro-2-bromobenzaldehyde was coupled with 2-aminothiophenol, 2-chlorodibenzothiazepine **33** was isolated in 59 % yield (Scheme 9).

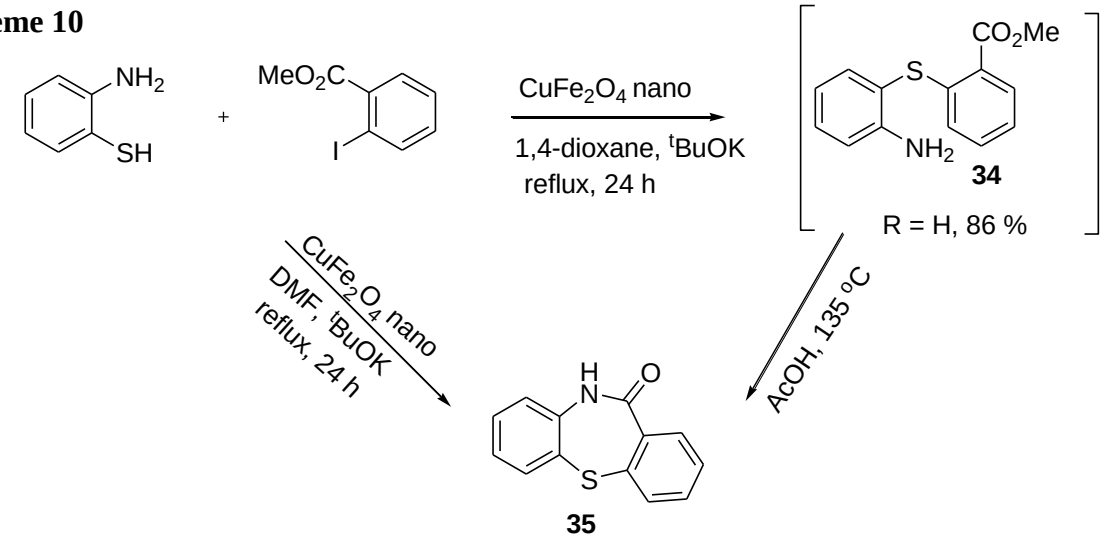
Scheme 9



33

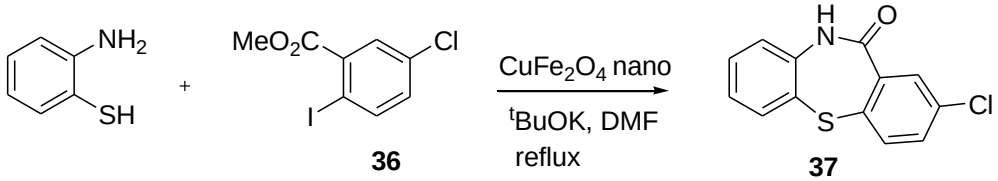
We were then interested towards the synthesis of functionalized dibenzothiazepines (e.g. dibenzothiazepinones).Thus, when methyl 2-iodobenzoate was employed, methyl 2-(2-aminophenylthio)benzoate **34** was obtained as the major product (86 %) and traces of dibenzothiazepine-11-one **35** (from TLC). However, on heating **34** at 135 °C in acetic acid we got quantitative yield of the desired product **35** (72 %). In order to access **35** directly from 2-aminothiophenol and methyl 2-iodobenzoate, reaction mixture was heated under reflux in DMF for 24 h during which moderated yield (60 %) was obtained (Scheme 10).

Scheme 10



The scope of the tandem C-N/C-S coupling was extended to the synthesis of substituted dibenzothiazepinone using 2-aminothiophenol as a coupling partner. The tandem C-N/C-S coupling between 2-aminothiophenol with 4-chloro-2-iodomethylbenzoate was carried out using $CuFe_2O_4$ as the catalyst in refluxing DMF. The tandem process resulted the substituted dibenzothiazepinones **37** in 53 % yield (Scheme 11).

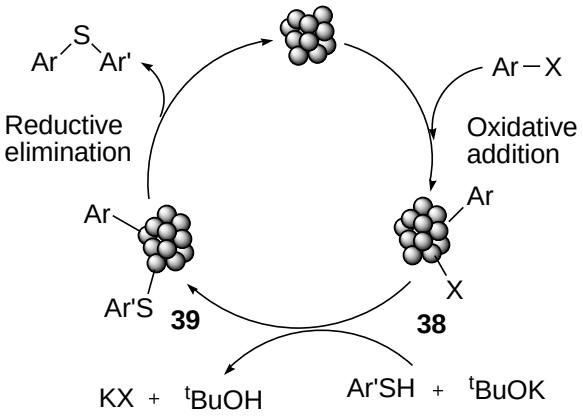
Scheme 11



Plausible Mechanism

Based on reactivity in the order iodobenzene > bromobenzene > chlorobenzene and regioselective experiments (Table 2, entries 2, 6, 9, 14), a plausible mechanism of oxidative addition followed by reductive elimination was proposed for the synthesis of C–S cross-coupling product. Initially, $CuFe_2O_4$ nanoparticles undergo oxidative addition with aryl halides (Ar-X) to form an intermediate **38**, which reacted with thiols in presence of ^tBuOK to form **39**. Finally **39** transformed into the required C-S cross-coupled product by reductive elimination reaction (Scheme 12). Due to high surface area and easier transfer of electrons, the copper ferrite nanoparticles may facilitate the oxidative addition reactions and also the polar 1,4-dioxane may prevent the aggregation of the nanoparticles and hence increases the catalyst solubility and stability during the reactions.[16]

Scheme 12



4.3. Reusability of the catalyst

The reusability of the copper ferrite nanoparticles have been studied by coupling thiophenol with 4-iodoacetophenone under the optimized conditions. After completion of the reaction, the catalyst was separated quantitatively (>95 %) by using a magnetic separator and washed with ethyl acetate followed by distilled water and acetone. Then, it was dried in hot air oven at 150 °C for 2 h and reused for the cross-coupling of thiophenol with 4-iodoacetophenone under our optimized reaction conditions. The catalytic behavior of $CuFe_2O_4$ was found to be unaltered (up to five consecutive cycles) with negligible leaching of Cu and Fe to the reaction

medium (Table 5). The weight percentage of copper and iron in the recovered catalyst was measured to be 4.08 mmol/g and 8.21 mmol/g, respectively (from ICP-MS).

Table 5. Reusability and leaching experiment over multiple run

Cycle	Recovered $CuFe_2O_4$ (%)	Yield of **3** (%)	Cu leakage (in ppm)	Fe leakage (in ppm)
1	-	95	0.25	0.08
2	96	93	0.22	0.02
3	95	93	0.20	0.02
4	95	92	0.06	0.01
5	94	90	0.05	0.01

Reaction conditions: 0.90 mmol of thiophenol, 1.80 mmol of 4-iodoacetophenone, 10 mol % of $CuFe_2O_4$ nanoparticles (for cycle 1 and the remaining recovered amount of the catalyst was used for subsequent cycles), 2.0 equiv of ^tBuOK, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

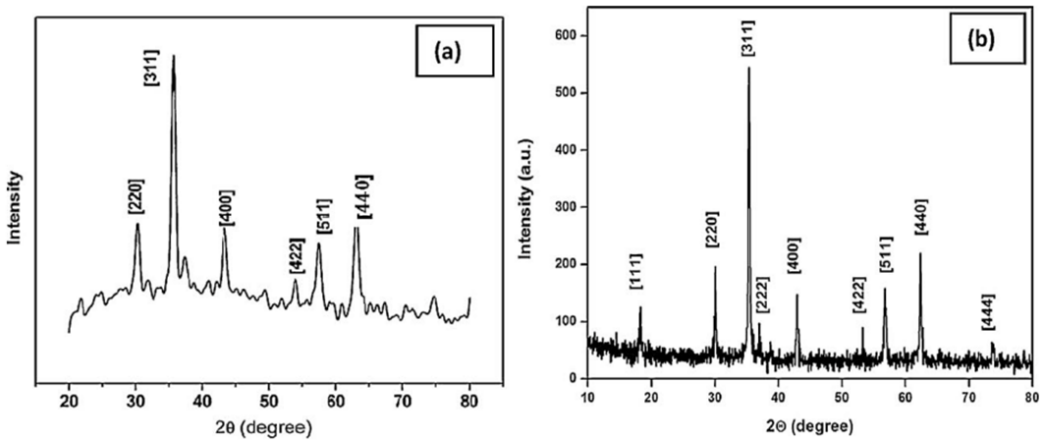


Fig. 2. XRD pattern of $CuFe_2O_4$ sample (a) freshly prepared; (b) recovered sample after S-arylation reaction

It was found from the XRD pattern of the recovered catalyst (Fig. 2) that although there is no change in phase but the crystallite size increases from 9 nm to 27 nm. As a result of which the saturation magnetization (Ms) at room temperature (Fig. 3A) increases from 23 emu g^{-1} to 32 emu g^{-1}. This increase in Ms could be attributed to the partial agglomeration of nanoparticles during catalytic reaction.[28] The SEM image (inset Fig. 3B) of the recovered catalyst shows that

the morphology as well as the dispersity of the catalyst is not affected even after the successful catalytic cycles.

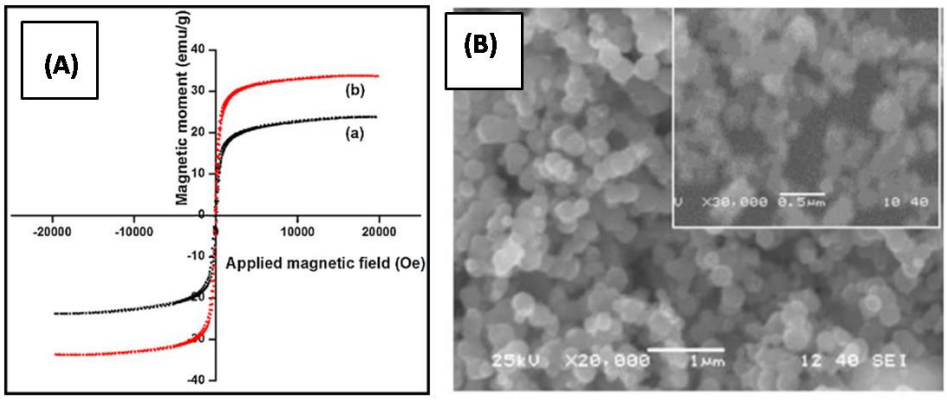


Fig. 3. (A) Field-dependent magnetization of (a) fresh $CuFe_2O_4$ catalyst and (b) recovered sample. (B) SEM image of fresh $CuFe_2O_4$ catalyst and recovered catalyst (inset)

4.4. Conclusion

$CuFe_2O_4$ nanoparticles were found to be efficient for the S-arylation reactions under ligand-free conditions whereas other ferrite nanoparticles were found to be ineffective. Our protocol was found to be tolerant to the cross-coupling of thiols with halides having different functional groups. Scope of this methodology has been extended to the one-pot synthesis of dibenzothiazepines for the first time. The magnetic nature of $CuFe_2O_4$ nanoparticles offers an advantage for easy, quick and quantitative separation of the heterogeneous catalysts from the reaction mixture. The use of $CuFe_2O_4$ nanoparticles for above cross-coupling reactions is found to be economic. Furthermore, the negligible leaching of Cu and Fe to reaction medium makes the reaction environmentally safe and thus may be adopted by the industries for large-scale synthesis.

4.5. Experimental

Procedure for preparation of Ethyl 2-mercaptobenzoate

A solution of 2-mercaptobenzoic acid (1 g, 6.4 mmol) and dry ethanol (5 mL) was refluxed for 24 h in presence of conc. H_2SO_4 (2 drops). The reaction mixture was then cooled to room temperature and excess of ethanol was removed by rotary evaporator. Water was then

added to the mixture followed by addition of dilute NaOH solution. The organic layer was collected by dichloromethane. The crude product was purified by column chromatography using petroleum ether and ethyl acetate as eluent to get 720 mg of ethyl 2-mercaptobenzoate (61%) as a solid.

MP: 97-99 °C. IR (KBr): 2980, 1701, 1647, 1583, 1457, 1434, 1365, 1286 $cm.^{-1}$.^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.11-8.06 (m, 1H), 7.79-7.75 (m, 1H), 7.45-7.39 (m, 1H), 7.28-7.22 (m, 1H), 4.47 (q, 2H, *J* = 14.4 Hz), 1.46 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.5 (s), 140.3 (s), 133.0 (d), 131.4 (d), 127.6 (s), 125.8 (d), 125.4 (d), 61.5 (t), 14.3 (q).

Procedure for preparation of benzo[d]thiazole-2-thiol[29]

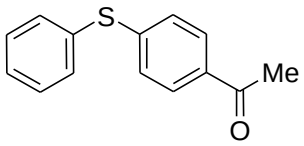
A mixture containing 2-aminothiophenol (1 g, 7.9 mmol) and NaOH (0.383 g) was stirred in a water-ethanol solution. To the above mixture CS_2 (0.729 g, 9.5 mmol) was added and the resulting solution was refluxed for 3 h. Charcoal was then added to the reaction mixture, refluxed for 10 minutes and filtered. The filtrate was heated at 60-70 ^{o}C, quenched with water and acetic acid. The product was separated and after cooling in the refrigerator the product benzo[d]thiazole-2-thiol was obtained (0.5 g).

MP: 170-172 °C. IR (KBr): 3103, 3075, 2963, 2890, 1591, 1538, 1493, 1453, 1422, 1370, 1317 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm):12.05 (s, 1H), 7.51-7.47 (m, 1H), 7.42-7.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 190.8 (s), 140.2 (s), 129.9 (s), 127.2 (d), 124.7 (d), 121.4 (d), 112.3 (d).

General procedure for S-arylation reactions

To a stirred solution of thiols (1 equiv), aryl halides (2 equiv) and ^{t}BuOK (2 equiv) in dry 1,4-dioxane, $CuFe_2O_4$ (10 mol %) was added and refluxed for 24 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and catalyst was separated by magnetic separator. The catalyst was washed with ethyl acetate. The combined ethyl acetate layer was washed with water (thrice), dried over anhydrous Na_2SO_4 and concentrated to yield the crude product, which was further purified by silica gel column chromatography using petroleum ether / ethyl acetate to yield the C-S coupling product **3-19**.

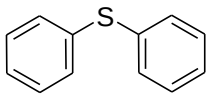
1-(4-(Phenylthio)phenyl)ethanone (3)[30]



Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 4-iodoacetophenone (446 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 197 mg (95 %) of the desired product **3** as a colourless solid.

MP: 64-66 °C. IR (KBr): 2994, 1675, 1586, 1555, 1472, 1397 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.88-7.82 (m, 2H), 7.58-7.50 (m, 2H), 7.46-7.36 (m, 3H), 7.26-7.20 (m, 2H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 197.1 (s), 144.9 (s), 134.4 (s), 133.9 (d), 132.0 (s), 129.7 (s), 128.9 (d), 128.8 (d), 127.4 (d), 26.5 (q). MS (ES) *m/z* (relative intensity) 229 ($[M+H]^+$ 100%). Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.65, H, 5.30, O, 7.01, S, 14.01; Found C, 73.47, H, 5.40, S, 14.02.

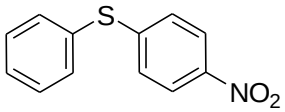
Diphenylsulfane (4)[12]



Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with iodobenzene (370 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 167 mg (98 %) of the desired product **4** as a yellow oil.

IR (neat): 3075, 1580, 1475, 1439, 738, 690 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.42-7.24 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 135.8 (s), 131.0 (d), 129.2 (d), 127.0 (d). MS (ES) *m/z* (relative intensity) 187 ($[M+H]^+$ 100%).

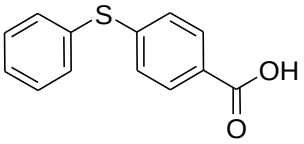
(4-Nitrophenyl)phenylsulfane (5)[12]



Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 4-iodonitrobenzene (451 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate) gave 180 mg (86 %) of the desired product **5** as a yellow solid.

MP: 55-56 °C. IR (KBr): 3063, 1654, 1620, 1572, 1503, 1474, 1439 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.10-8.02 (m, 2H), 7.60-7.52 (m, 2H), 7.50-7.42 (m, 3H), 7.22-7.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 148.5 (s), 145.3 (s), 134.8 (d), 130.3 (s), 130.0 (d), 129.7 (d), 126.6 (d), 124.0 (d). Anal. Calcd. for $C_{12}H_9NO_2S$: C, 62.32, H, 3.92, N, 6.06, O, 13.84, S, 13.86; Found C, 62.45, H, 3.87, N, 6.10, S, 13.89.

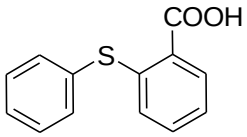
4-Phenylthiobenzoic acid (6)



Following the general procedure thiophenol (88 mg, 0.80 mmol) was coupled with 4-iodobenzoic acid (100 mg, 0.40 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 80 mg (87 %) of the desired product **6** as a colourless solid.

MP: 172 °C. IR (KBr): 3414, 1679, 1588, 1480, 1423, 139 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ(ppm): 7.95 (d, 2H, *J* = 8.5 Hz), 7.53-7.38 (m, 5H), 7.20 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 171.4, 146.0, 134.0, 131.8, 130.6, 129.7, 128.9, 127.1, 126.3. Anal. Calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; Found C, 67.54; H, 4.20.

2-Phenylthiobenzoic acid (7) [12]

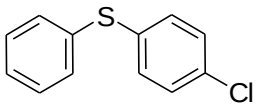


Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with iodobenzoic acids (449 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography

(eluent: petroleum ether : ethyl acetate) gave 188 mg (90 %) of the desired product **7** as a colourless solid.

MP: 166-167 °C IR (KBr): 1678, 1595, 1546, 1461, 1435 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 10.19 (bs, 1H), 8.16 (d, 1H, *J* = 8.0 Hz), 7.62-7.14 (m, 7H), 6.82 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): δ 171.9 (s), 144.6 (s), 135.9 (d), 133.1 (d), 132.2 (d), 132.0 (s), 129.8 (d), 129.3 (d), 127.1 (d), 125.5 (s), 124.3 (d). Anal. Calcd. for $C_{13}H_{10}O_2S$: C, 67.80, H, 4.38, O, 13.90, S, 13.92: Found C, 67.70, H, 4.46, S, 13.85. MS (EI) *m/z* (relative intensity) 230 ($[M],^{+}$ 100%).

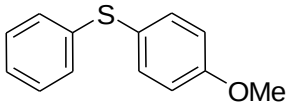
(4-Chlorophenyl)(phenyl)sulfane (8)



Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 4-iodochlorobenzene (431 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 176 mg (88 %) of the desired product **8** as a colourless liquid.

IR (neat): 3057, 1581, 1553, 1535, 1515, 1472 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.46-7.30 (m, 9H) ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 135.2 (s), 134.7 (s), 133.0 (s), 132.1 (d), 131.4(d), 129.4 (d), 129.4 (d), 127.5 (d).

(4-Methoxyphenyl)(phenyl)sulfane (9)[30]

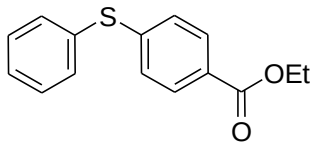


Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 4-iodoanisole (204 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 165 mg (83%) of the desired product **9** as a colourless liquid.

IR (neat): 3075, 2956, 2932, 1590, 1491, 1440 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.48-7.42 (m, 2H), 7.30-7.16 (m, 5H), 6.98-6.90 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$),

δ (ppm): 159.8 (s), 138.6 (s), 135.4 (d), 128.9 (d), 128.1 (d), 125.7 (d), 124.2 (s), 115.0 (d), 55.4 (q). Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82; Found C, 72.24; H, 5.72; S, 14.81.

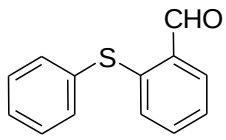
Ethyl-4-(phenylthio)benzoate (10)[30]



Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 4-bromoethylbenzoate (415 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 196 mg (76 %) of the desired product **10** as a colourless oil.

IR (neat): 3058, 2980, 1712, 1592, 1562, 1475, 1440 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.96-7.90 (m, 2H), 7.52-7.48 (m, 2H), 7.44-7.38 (m, 3H), 7.26-7.20 (m, 2H), 4.37 (q, 2H, *J* = 8 Hz), 1.39 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.22 (s), 144.1 (s), 133.6 (d), 132.5 (s), 130.0 (d), 129.6 (d), 128.6 (d), 127.8 (s), 127.6 (d), 60.9 (t), 14.3 (q). Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74, H, 5.46, O, 12.39, S, 12.41; Found C, 69.64, H, 5.36, S, 12.48. MS (EI) *m/z* (relative intensity) 258 ($[M],^{+}$ 100%).

2-(Phenylthio)benzaldehyde (11)

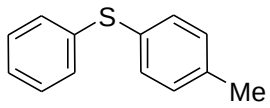


Following the general procedure thiophenol (100 mg, 0.90 mmol) was coupled with 2-bromobenzaldehyde (335 mg, 1.81 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 139 mg (72 %) of the desired product **11** as a colourless oil.

IR (neat): 3057, 2851, 2737, 1693, 1584, 1557, 1475, 1439 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 10.38 (s, 1H), 7.87-7.86 (d, 1H), 7.46-7.30 (m, 7H), 7.12-7.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 191.4 (s), 141.5 (s), 134.1 (d), 133.7 (s), 133.2 (s), 133.1 (d), 131.2 (d),

130.3 (d), 129.7 (d), 128.4 (d), 126.3 (d). Anal. Calcd. for $C_{13}H_{10}OS$: C, 72.87, H, 4.70, O, 7.47, S, 14.96; Found C, 72.81, H, 4.68, S, 14.93.

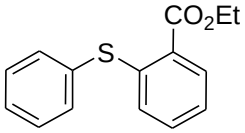
***Phenyl(p-tolyl)sulfane (12)*[30]**



Following the general procedure 4-methylbenzenthiol (100 mg, 0.71 mmol) was coupled with iodobenene (291 mg, 1.42 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 123 mg (80 %) of the desired product **12** as a colourless oil.

IR (neat): 2920, 1580, 1491, 1476, 1437 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.28 (d, 2H, *J* = 8.4 Hz), 7.20-7.15 (m, 2H), 7.12 (d, 2H, *J* = 8.4 Hz), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 137.5 (s), 137.1 (s), 132.2 (d), 130.0 (d), 129.7 (d), 129.0 (d), 128.5 (s), 126.3 (d), 21.1 (q). Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95, H, 6.04, S, 16.01; Found C, 77.89, H, 6.14, S, 15.08.

Ethyl-2-(phenylthio)benzoate (13)

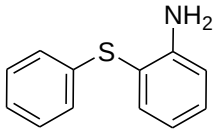


Following the general procedure ethyl 2-mercaptobenzoate (100 mg, 0.54 mmol) was coupled with iodobenzene (224 mg, 1.09 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 110 mg (78 %) of the desired product 1**3** as a colourless oil.

IR (neat): 3058, 2980, 1711, 1586, 1562, 1461, 1437 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.04-7.99 (m, 1H), 7.60-7.54 (m, 2H), 7.48-7.42 (m, 3H), 7.28-7.20 (m, 1H), 7.18-7.10 (m, 1H), 6.86-6.80 (m, 1H), 4.372 (q, 2H, *J* = 6.8 Hz), 1.44 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.5 (s), 143.0 (s), 135.5 (d), 132.6 (s), 132.2 (d), 130.9 (d), 129.7 (d),

129.0 (d), 127.4 (d), 127.1 (s), 124.2 (d), 61.2 (t), 14.3 (q). Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74, H, 5.46, O, 12.39, S, 12.41; Found C, 69.78, H, 5.40, S, 12.45.

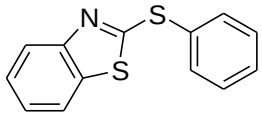
2-(Phenylthio)benzamine (14)



Following the general procedure 2-aminothiophenol (100 mg, 0.79 mmol) was coupled with iodobenzene (325 mg, 1.59 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 137 mg (85 %) of the desired product **14** as a colourless oil.

IR (neat): 3467, 3368, 3058, 1608, 1581, 1477, 1441 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.57-7.54 (t, 1H), 7.34-7.27 (m, 3H), 7.20-7.16 (m, 3H), 6.86-6.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (s), 137.5 (d), 136.9 (s), 131.2 (d), 129.1 (d), 126.4 (d), 125.5 (d), 118.8 (d), 115.4 (d), 114.2 (s).

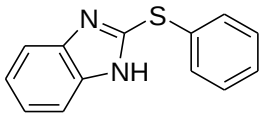
2-(Phenylthio)benzo[d]thiazole (15)[12]



Following the general procedure benzo[d]thiazole-2-thiol (100 mg, 0.59 mmol) was coupled with iodobenzene (244 mg, 1.19 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 119 mg (82 %) of the desired product **15** as a colourless liquid.

IR (neat): 3058, 1579, 1526, 1456, 1425 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.94-7.90 (d, 1H), 7.77-7.76 (d, 2H), 7.76-7.75 (d, 1H), ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 169.7 (s), 153. 9 (s), 135.5 (s), 135.4 (d), 130.5 (d), 129.9 (d), 129.9 (s), 126.2 (d), 124.3 (d), 121.9 (d), 120.8 (d). MS (EI) *m/z* (relative intensity) 243 ([M]$^+$, 100%).

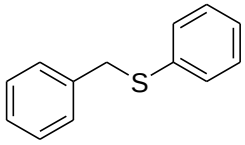
2-(Phenylthio)benzo[d]imidazole (16)



Following the general procedure benzo[d]imidazole-2-thiol (100 mg, 0.66 mmol) was coupled with iodobenzene (271 mg, 1.33 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate) gave 151 mg (88 %) of the desired product **16** as a colourless solid.

MP: 105 °C. IR (KBr): 3043, 2958, 1616, 1502, 1474, 1439 $cm.^{-1}$. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 12.83 (bs, 1H), 7.60-4.40 (m, 7H), 7.22-7.12 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 131.7, 131.6, 130.0, 128.6, 123.0, 122.0, 118.8, 111.5.

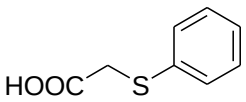
Benzylphenylsulfane (17)[31]



Following the general procedure benzylthiol (100 mg, 0.80 mmol) was coupled with iodobenzene (328 mg, 1.61 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate) gave 140 mg (86 %) of the desired product **17** as a colourless solid.

MP: 41 °C. IR (KBr): 3449, 3059, 1480, 1454, 1438, 1090 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.38-7.20 (m, 10H), 4.16 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm):137.4 (s), 136.3 (s), 129.8 (d), 128.8 (d), 128.8 (d), 128.5 (d), 127.2 (d), 126.3 (d), 39.0 (t). MS (ES) *m/z* (relative intensity) 201 ($[M+H]^+$ 75%), 223 ($[M+Na]^+$ 100%).

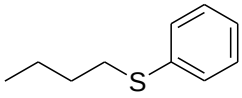
2-(Phenylthio)acetic acid (18)



Following the general procedure 2-mercaptoacetic acid (100 mg, 1.08 mmol) was coupled with iodobenzene (442 mg, 2.17 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether : ethyl acetate) gave 80 mg (40 %) of the desired product **18** as a colourless solid.

MP: 62 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 11.61 (bs, 1H) 7.46-7.40 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.22 (m, 1H), 3.7 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 176.4 (s), 134.6 (s), 129.9 (d), 129.2 (d), 127.2 (d), 36.5 (t).

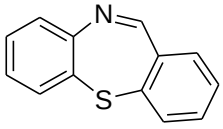
***Butyl(phenyl)sulfane (19)*[32]**



Following the general procedure butanthiol (100 mg, 1.10 mmol) was coupled with iodobenzene (206 mg, 2.20 mmol). The crude mass was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate) gave 147 mg (80%) of the desired product **19** as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1H NMR ($CDCl_3$, 400 MHz) 7.32-7.24 (m, 4H), 7.16-7.14 (m, 1H), 2.88 (t, 2H, *J* = 7.6 Hz), 1.64-1.59 (m, 2H), 1.47-1.41 (m, 2H), 0.90 (t, 3H, *J* = 2.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 137.5, 137.1, 130.3, 128.9, 127.5, 125.6, 33.2, 31.3, 22.0, 13.7. Anal. Calcd. for $C_{10}H_{14}S$: C, 72.23, H, 8.49, S, 19.28; Found C, 72.13, H, 8.42, S, 19.37.

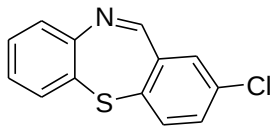
***Dibenzo[b,f][1,4]thiazepine (32)*[33]**



Compound **32** was obtained by coupling 2-aminothiophenol (100 mg, 0.8 mmol) and 2-bromobenzaldehyde (162 mg, 0.88 mmol) over a period of 24 h under reflux in 1,4-dioxane in 80 % (135 mg) yield.

MP: 115 °C. IR (KBr): 3054, 2921, 2845, 1627, 1580, 1456 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.92 (s, 1H), 7.48-7.30 (m, 7H), 7.22- 7.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 162.30 (d), 148.51 (s), 139.36 (s), 137.20 (s), 132.78 (d), 131.63 (d), 131.49 (d), 129.42 (d), 129.28 (d), 128.86 (s), 128.25 (d), 127.23 (d), 126.93 (d). MS (EI) *m/z* (relative intensity) 211 ($[M],^{+}$ 100%).

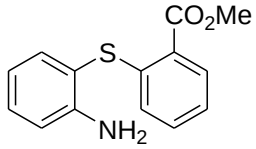
2-Chlorodibenzo[b,f][1,4]thiazepine (33)



Compound **33** was obtained by coupling 2-aminothiophenol (100 mg, 0.8 mmol) and 2-iodo-5-chlorobenzaldehyde (206 mg, 0.88 mmol) over a period of 24 h under reflux in 1,4-dioxane in 59 % (115 mg) yield as a liquid.

IR (neat): 2922, 1627, 1574, 1552, 1457, 1431 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.84 (s, 1H), 7.46-7.30 (m, 6H), 7.23-7.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 160.5 (d), 148.3 (s), 138.2 (s), 137.8 (s), 134.5 (s), 132.8 (d), 132.7 (d), 131.3 (d), 129.5 (d), 129.1 (d), 128.3 (s), 127.4 (d), 126.9 (d).

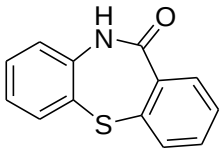
Methyl-2-(2-aminophenylthio)benzoate (34)



Compound **34** was obtained by coupling 2-aminothiophenol (100 mg, 0.8 mmol) and methyl-2-iodobenzoate (230 mg, 0.88 mmol) over a period of 24 h under reflux in 1,4-dioxane in 86% (178 mg) yield as a solid.

MP: 95-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.10-8.00 (m, 1H), 7.50-7.45 (m, 1H), 7.32-7.22 (m, 2H), 7.16-7.10 (m, 1H), 6.85-6.75 (m, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9 (s), 149.5 (s), 141.5 (s), 138.0 (d), 132.6 (d), 131.6 (d), 131.4 (d), 126.3 (s), 125.8 (d), 124.2 (d), 118.9 (d), 115.3 (d), 113.6 (s), 52.2 (q).

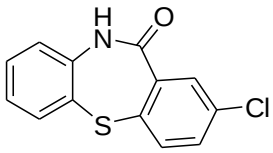
Dibenzo[b,f][1,4]thiazepin-11(10H)-one (35)[34].



Compound **35** was obtained by coupling 2-aminothiophenol (100 mg, 0.8 mmol) and methyl-2-iodobenzoate (230 mg, 0.88 mmol) over a period of 24 h under reflux in DMF in 60 % (116 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$:DMSO-d_6 1:1), δ (ppm): 8.76 (bs, 1H), 7.90-7.84 (m, 1H), 7.62-7.56 (m, 1H), 7.55-7.50 (m, 1H), 7.44-7.36 (m, 2H), 7.35-7.30 (m, 1H), 7.22- 7.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 1:1), δ (ppm): 169.8 (s), 139.3 (d), 137.3 (d), 136.9 (s), 133.0 (d), 132.2 (d), 131.8 (d), 131.8 (s), 130.2 (s), 129.7 (d), 128.7 (d), 126.0 (d), 122.6 (d). MS (EI) *m/z* (relative intensity) 227 ($[M]^+$, 100%).

2-Chlorodibenzo[b,f][1,4]thiazepin-11(10H)-one (37)[35]



Compound **37** was obtained by coupling 2-aminothiophenol (100 mg, 0.8 mmol) and methyl-4-chloro-2-iodobenzoate (474 mg, 1.6 mmol) over a period of 24 h under reflux in DMF in 53 % (108 mg) yield.

MP: 256-258 °C. IR (KBr): 3283, 3161, 3030, 2954, 1643, 1576, 1551, 1478 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.86 (s, 1H), 7.84 (d, 1H, *J* = 2.4 Hz), 7.60-7.56 (m, 1H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.40-7.31 (m, 2H,), 7.23-7.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 168.5 (s), 139.1 (s), 138.3 (s), 135.8 (s), 135.0 (s), 133.0 (d), 132.1 (d), 131.7 (d), 129.9 (d), 129.8 (d), 126.2 (d), 122.8 (d).

4.6. References

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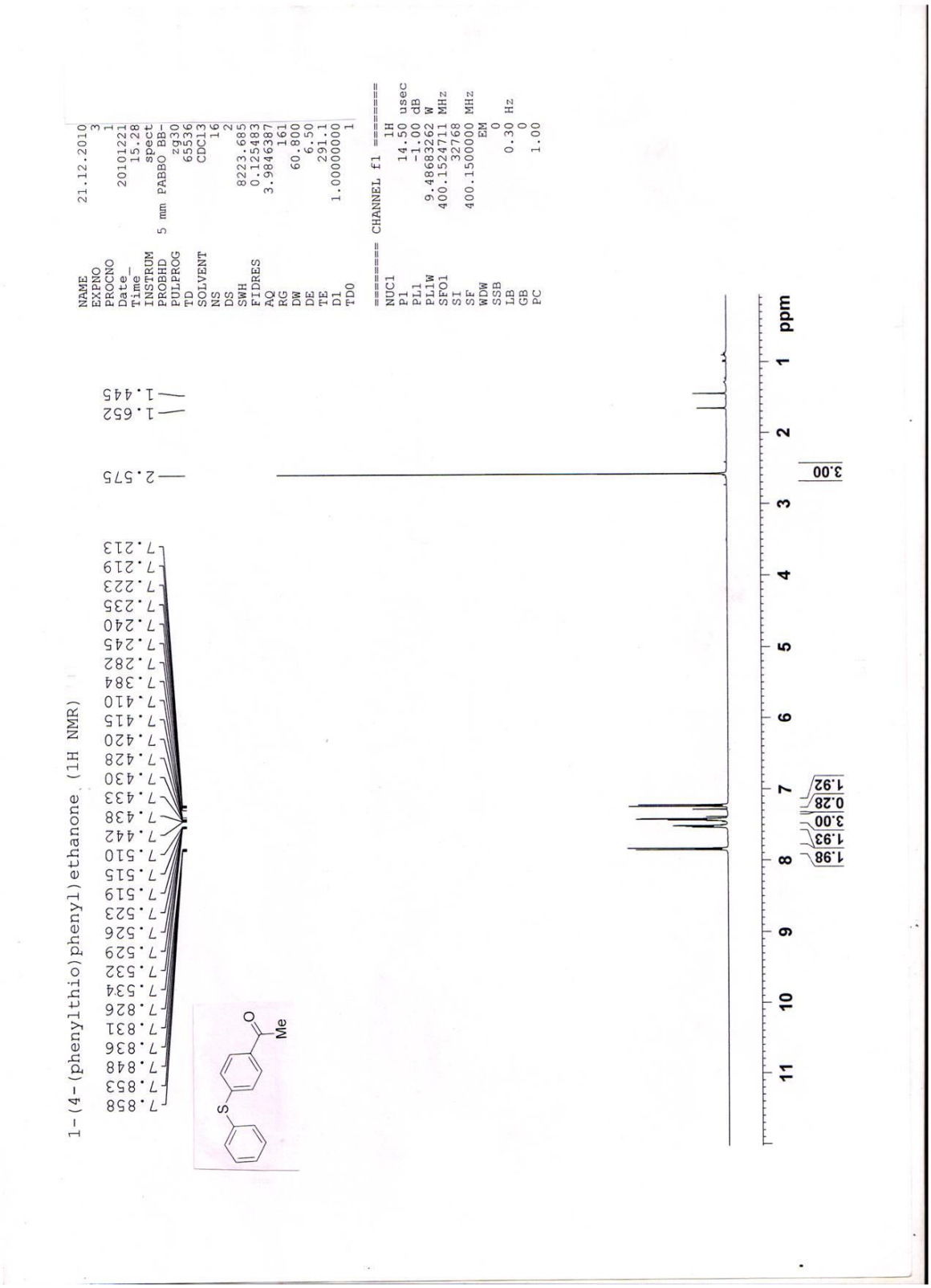
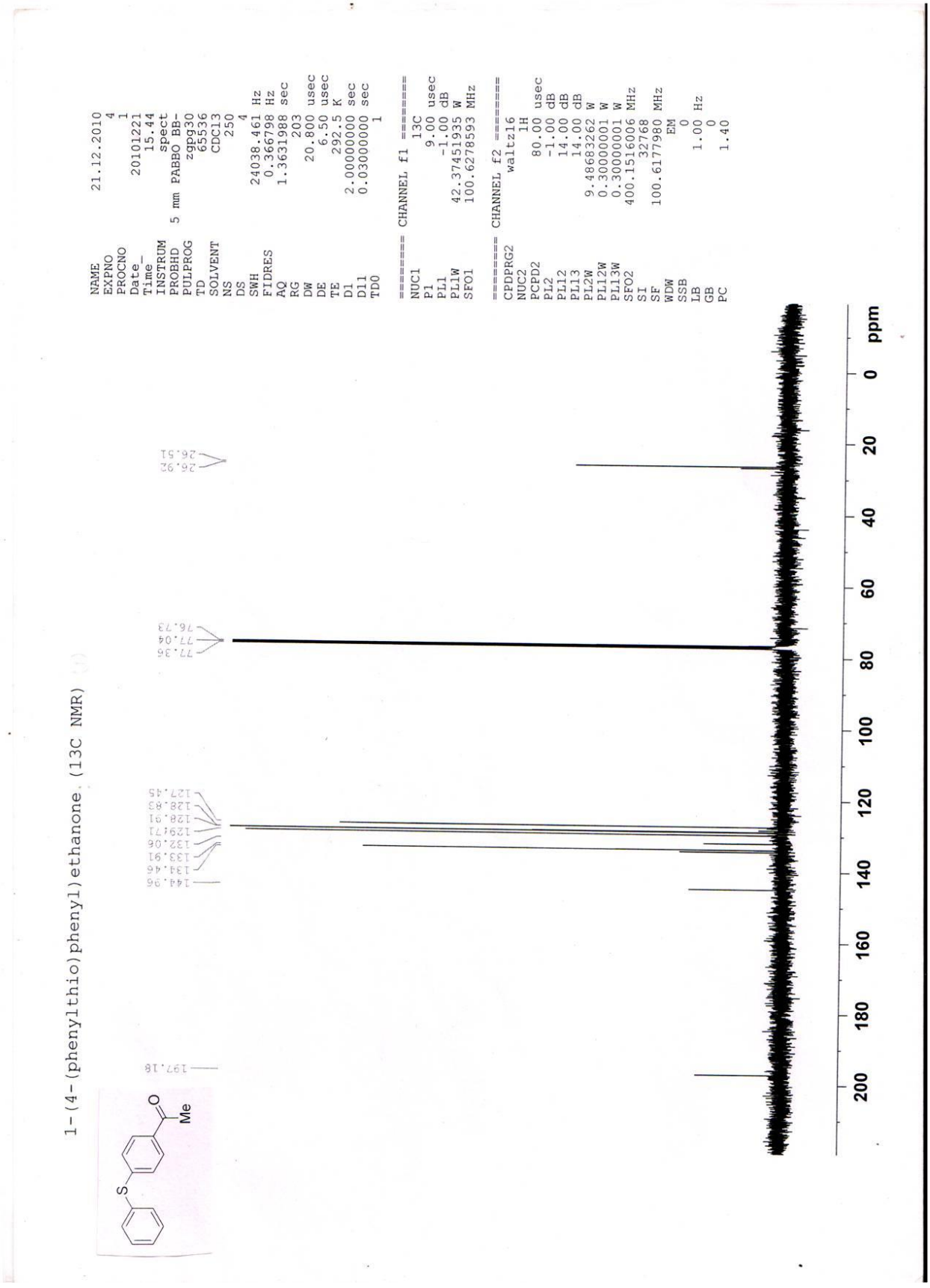
4.7. Selected NMR spectra

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D11 0.03000000 sec
TD0 1
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PCPD2 80.00 usec
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PL12 14.00 dB
PL13 14.00 dB
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PL12W 0.30000001 W
PL13W 0.30000001 W
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SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
197.18
144.96
134.46
133.91
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129.71
128.91
128.85
127.45
77.36
77.04
76.73
26.92
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O
Me
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160
140
120
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80
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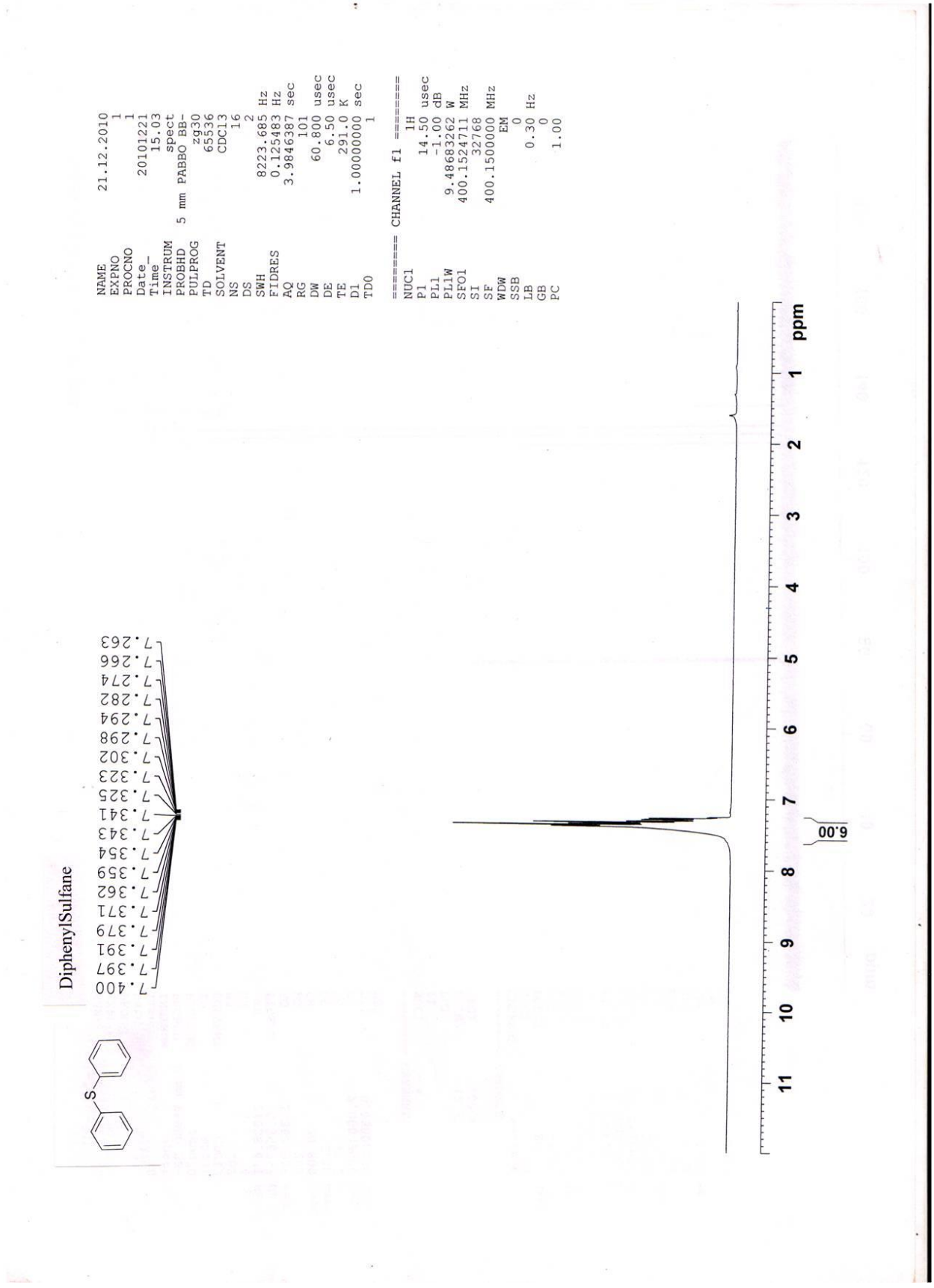
40
20
0
ppm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7.343
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7.325
7.323
7.302
7.298
7.294
7.282
7.274
7.266
7.263
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TD0 1
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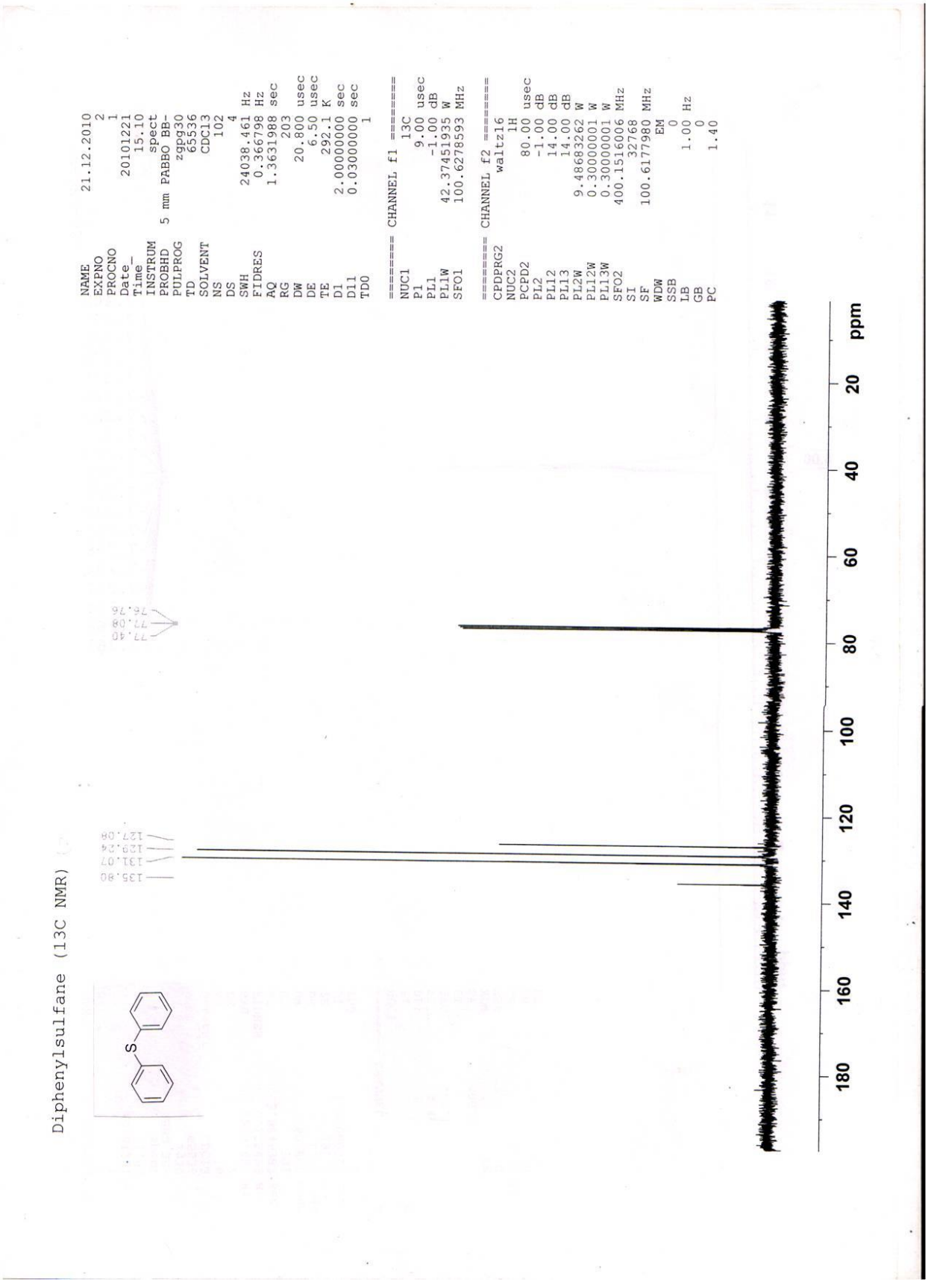
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76.76
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PROCNO 1
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FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
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PL1 -1.00 dB
PL1W 42.37451935 W
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PL13 14.00 dB
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PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
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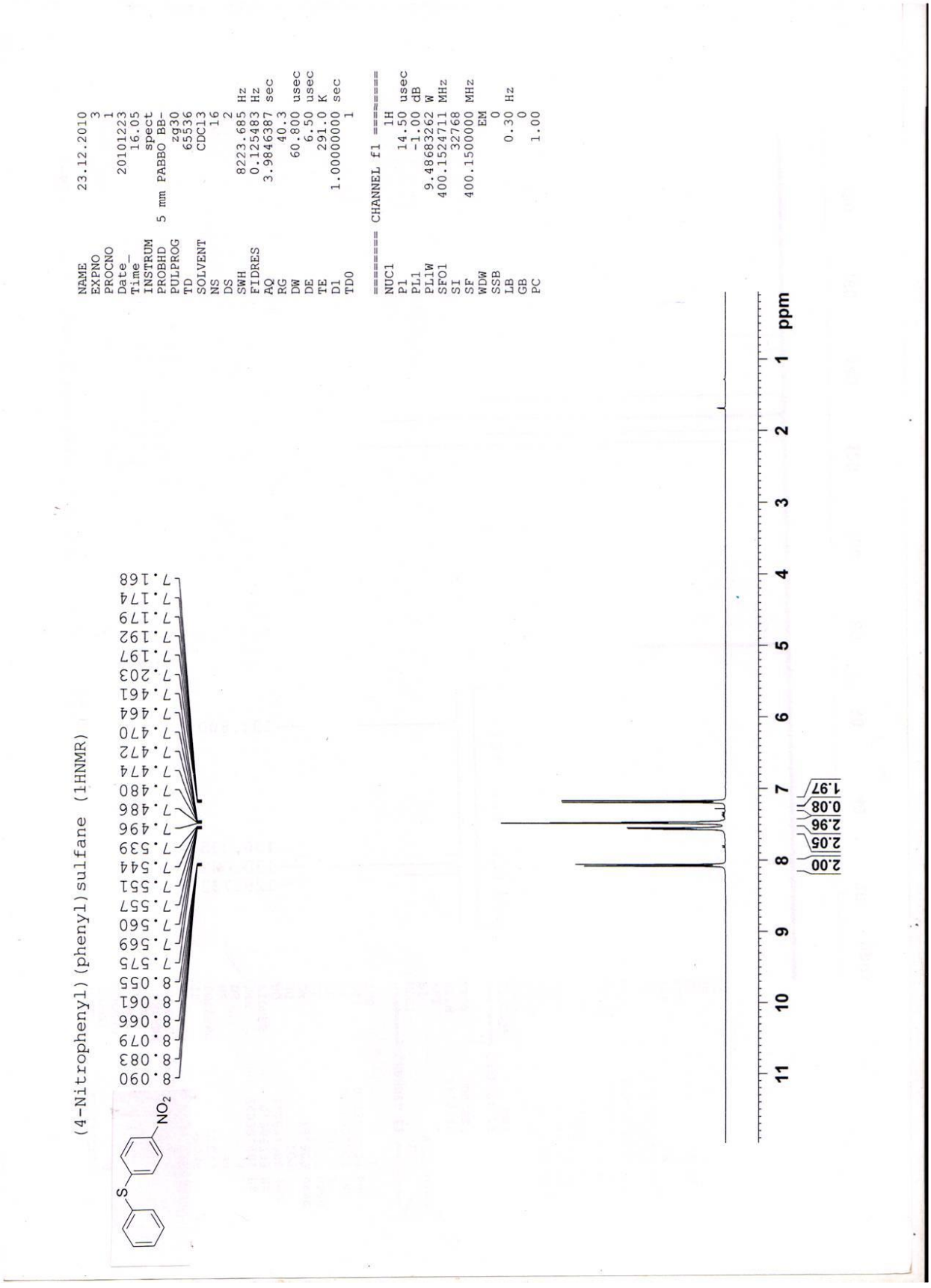
180 160 140 120 100 80 60 40 20 ppm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7.557
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7.464
7.461
7.203
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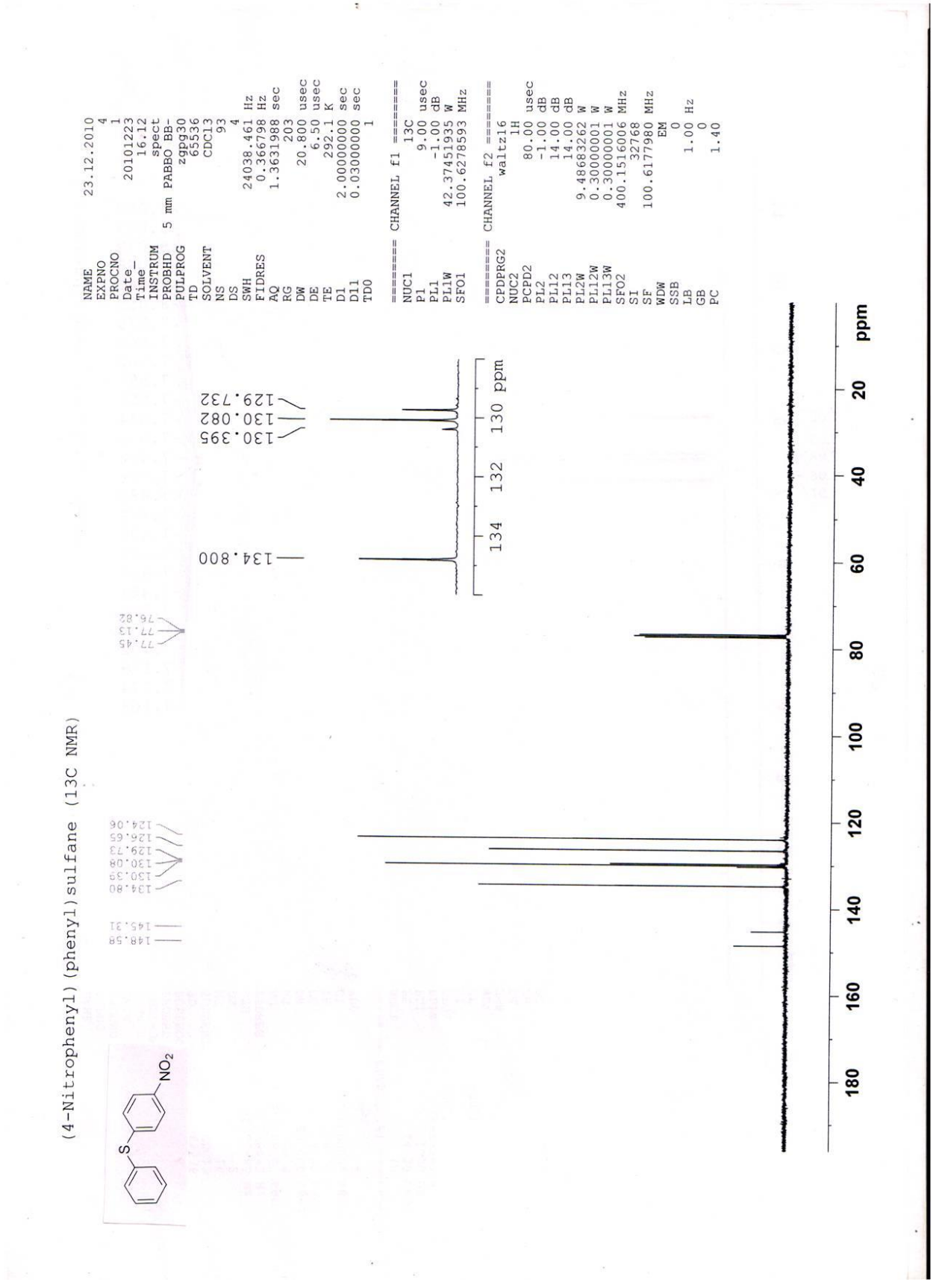
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SOLVENT CDCl3
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DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
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P1 9.00 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 100.6278593 MHz
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PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
PL2W 9.48683262 W
PL12W 0.30000001 W
PL13W 0.30000001 W
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SI 32768
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148.58
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124.06
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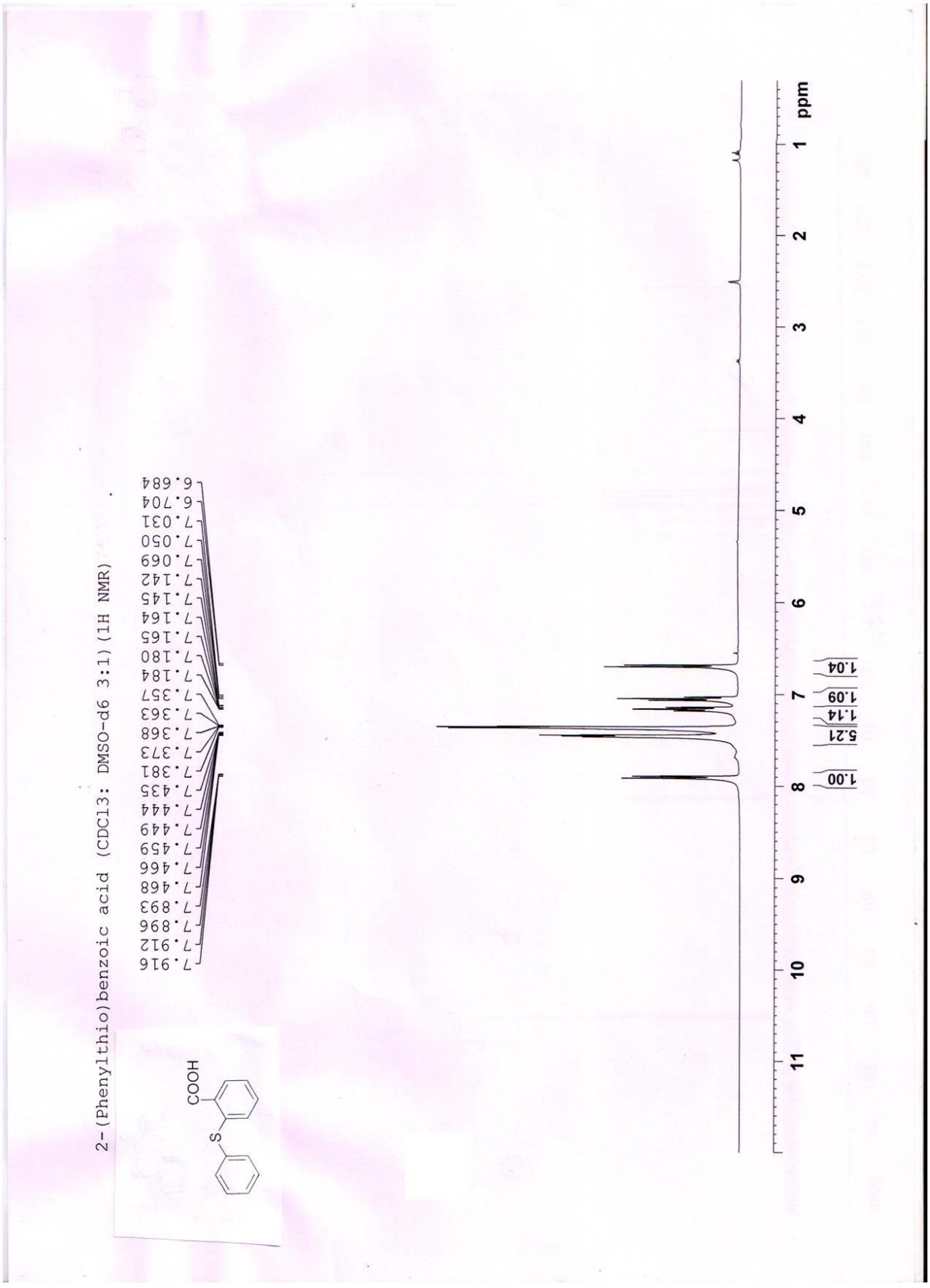
180 160 140 120 100 80 60 40 20 ppm
S
NO2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7.069
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COOH
S
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5.21
1.14
1.09
1.04
ppm


2-(Phenylthio)benzoic acid (CDCL3:DMSO-d6 (3:1)(13C NMR)
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129.20
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124.32
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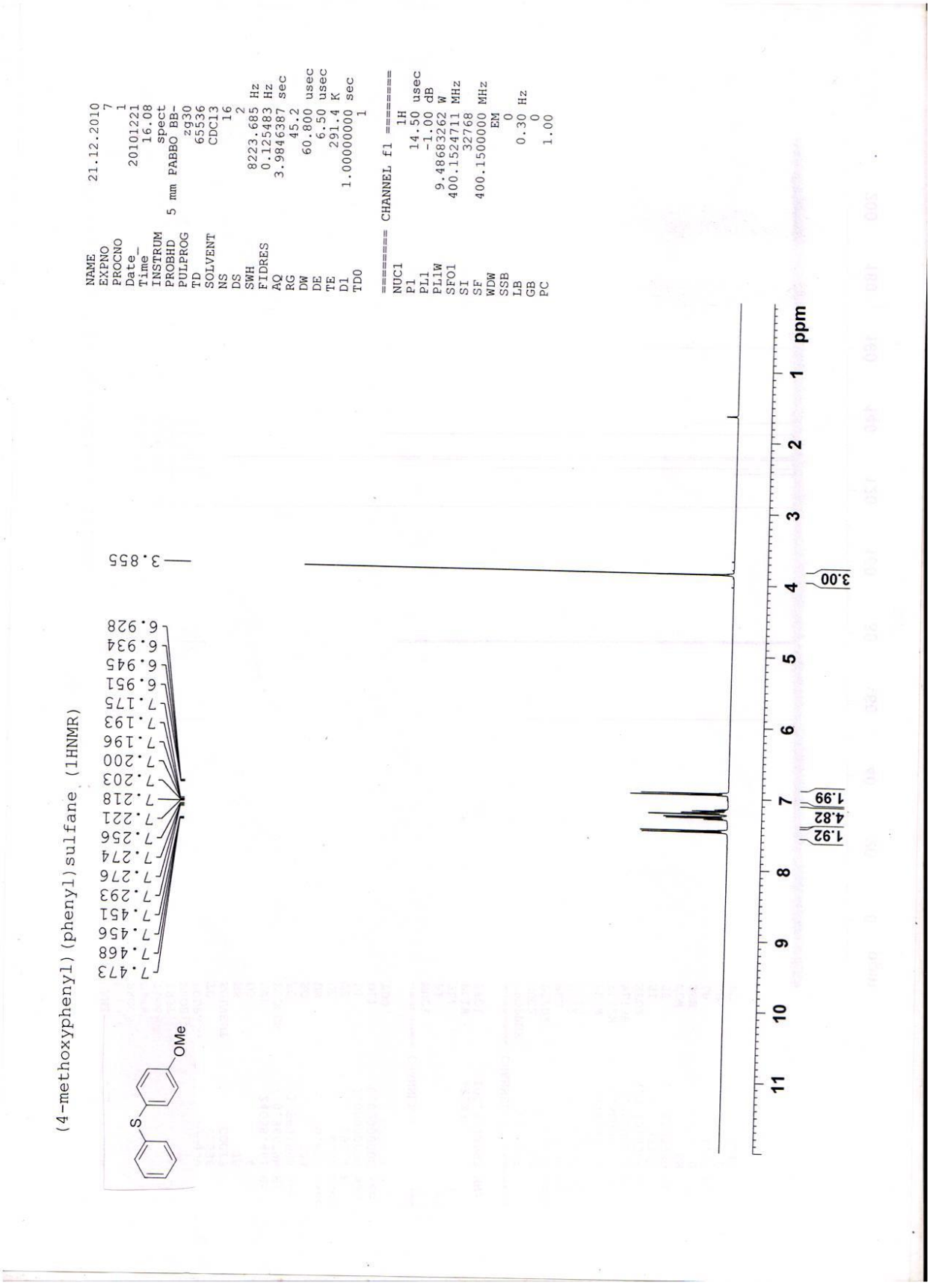
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7.221
7.218
7.203
7.200
7.196
7.193
7.175
6.951
6.945
6.934
6.928
3.855
NAME 21.12.2010
EXPNO 7
PROCNO 1
Date_ 20101221
Time_ 16.08
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SOLVENT CDC13
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DS 2
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FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 45.2
DW 60.800 usec
DE 6.50 usec
TE 291.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.50 usec
PL1 -1.00 dB
PL1W 9.48683262 W
SFO1 400.1524711 MHz
SI 32768
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 ppm
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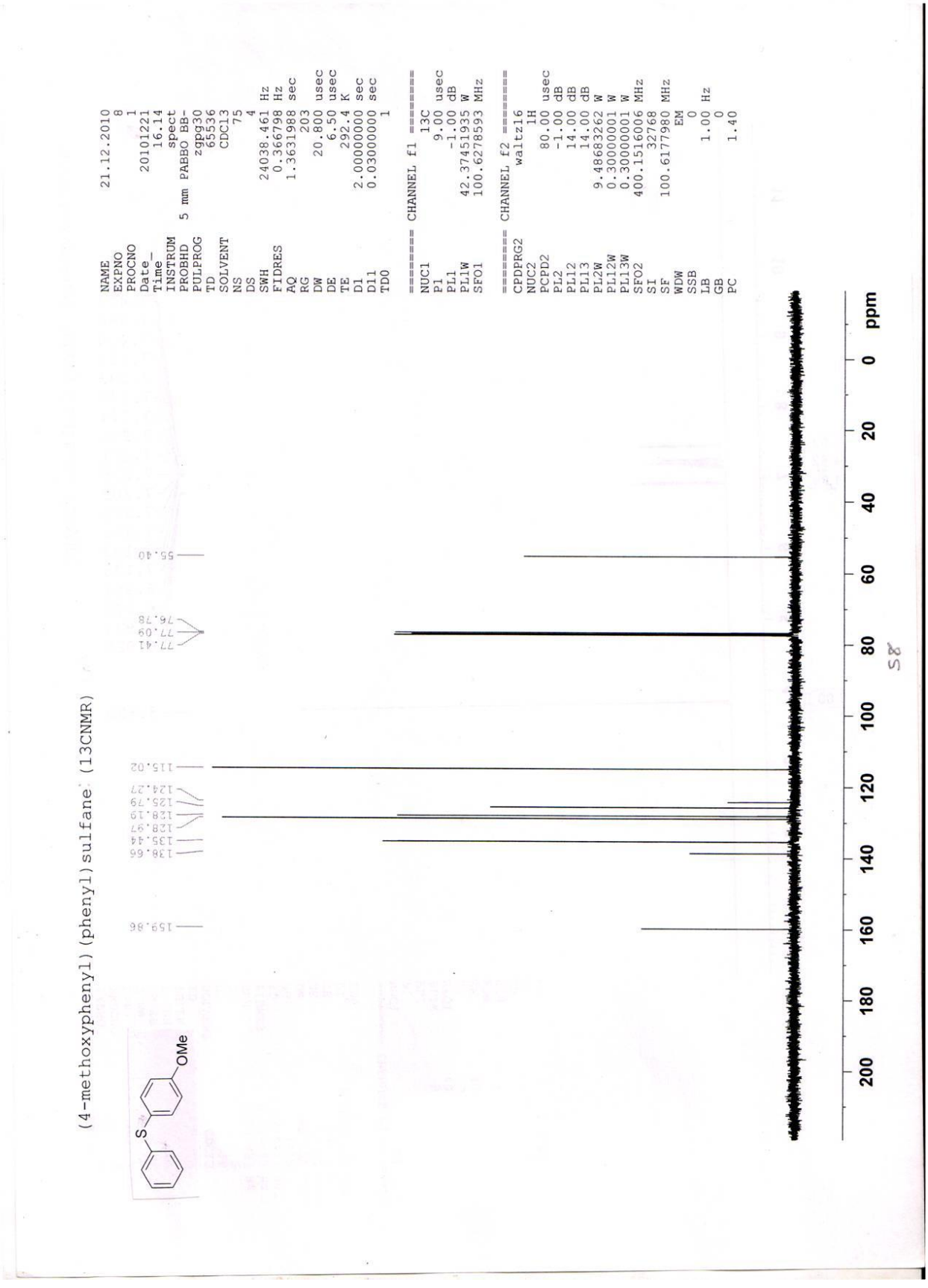
1.92
4.82
1.99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Time 16.14
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TD 65536
SOLVENT CDCl3
NS 75
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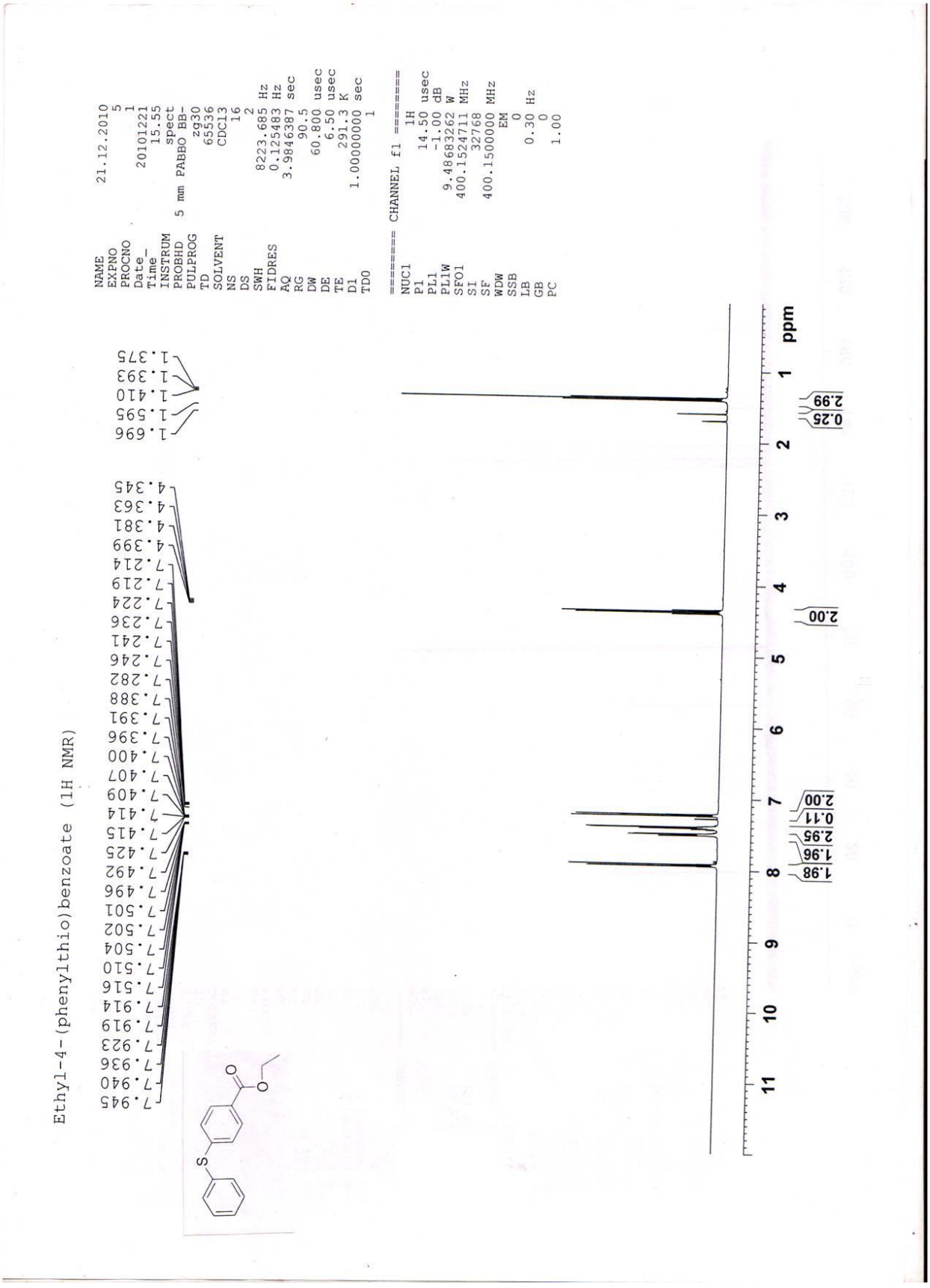
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 100.6278593 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
PL2W 9.48683262 W
PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
159.86
138.66
135.44
128.97
128.19
125.79
124.27
115.02
77.41
77.09
76.78
56.40
200 180 160 140 120 100 80 60 40 20 0 ppm
S8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PROCNO 1
Date_ 20101221
Time_ 15.55
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 90.5
DW 60.800 usec
DE 6.50 usec
TE 291.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.50 usec
PL1 -1.00 dB
PL1W 9.48683262 W
SFO1 400.1524711 MHz
SI 32768
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.945
7.940
7.936
7.923
7.919
7.914
7.516
7.510
7.504
7.502
7.501
7.496
7.492
7.425
7.415
7.414
7.409
7.407
7.400
7.396
7.391
7.388
7.282
7.246
7.241
7.236
7.224
7.219
7.214
4.399
4.381
4.363
4.345
1.696
1.595
1.410
1.393
1.375
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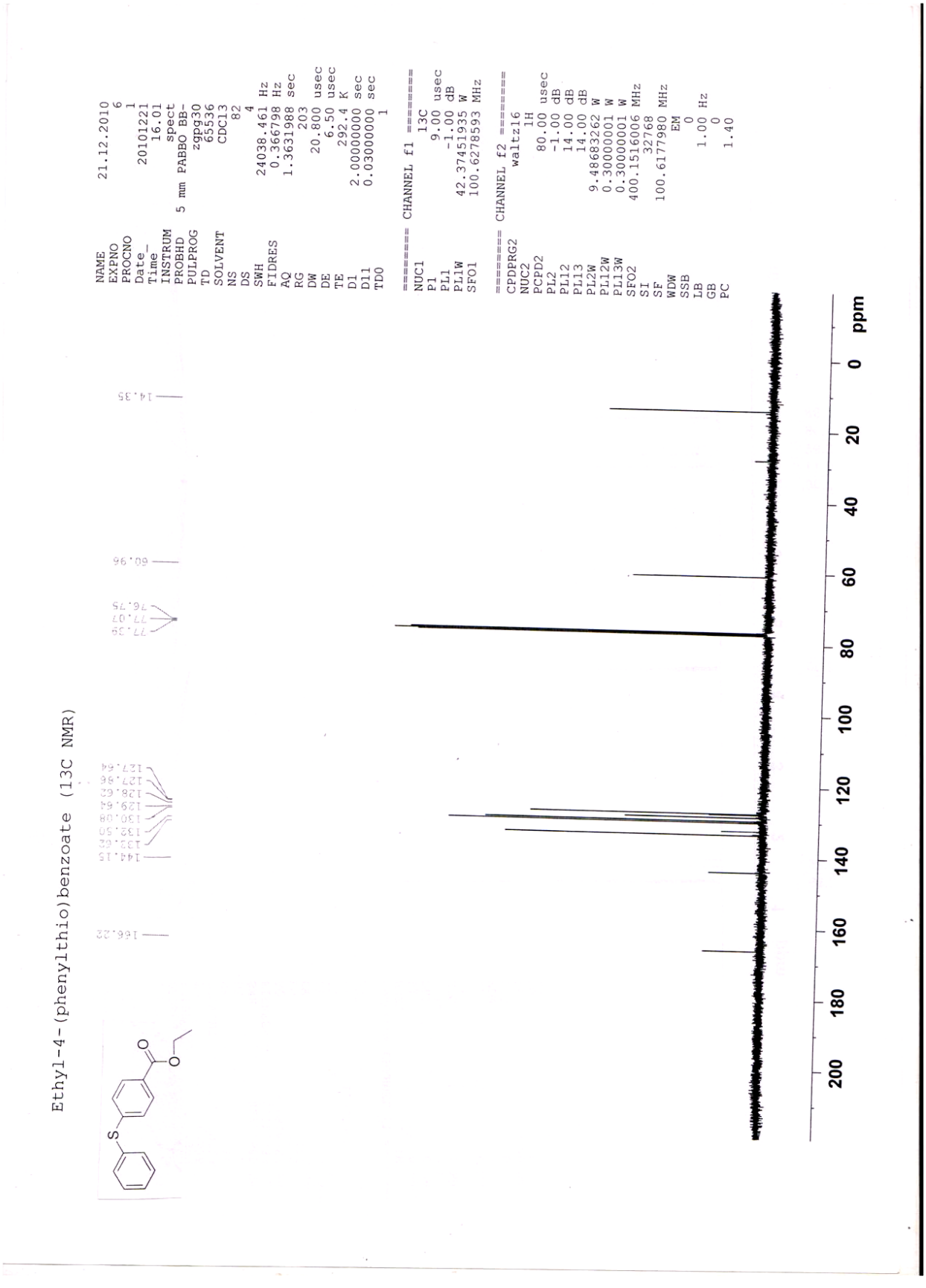
2.99
2.00
1.98
1.96
2.95
0.11
2.00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PROCNO 1
Date_ 20101221
Time_ 16.01
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 82
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 100.6278593 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
PL2W 9.48683262 W
PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
166.22
144.15
133.62
132.50
130.08
129.64
128.62
127.86
127.64
77.39
77.07
76.75
60.96
14.35
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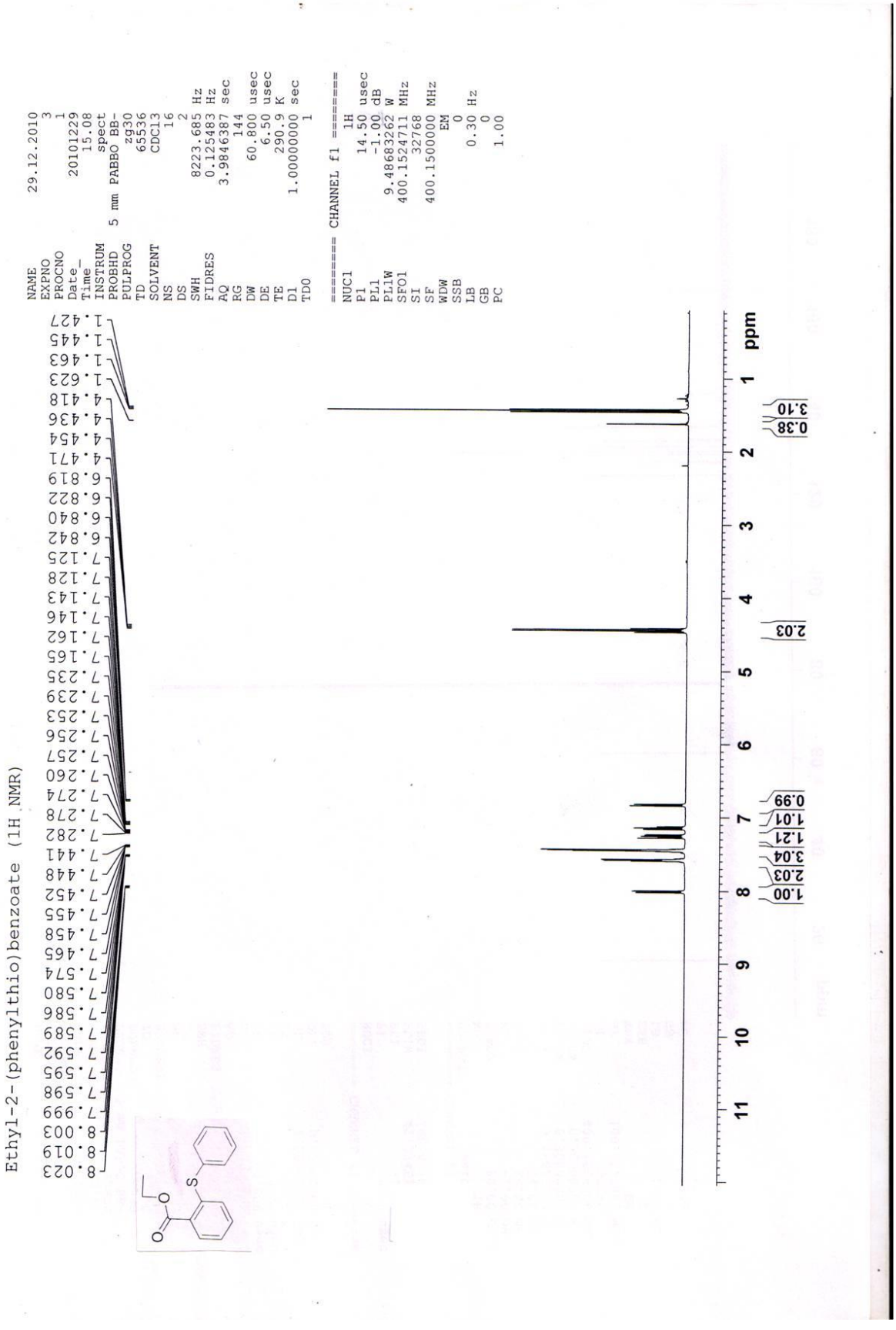
180
160
140
120
100
80
60
40
20
0
ppm


Ethyl-2-(phenylthio)benzoate (1H NMR)
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PROCNO 1
Date_ 20101229
Time_ 15.08
INSTRUM spect
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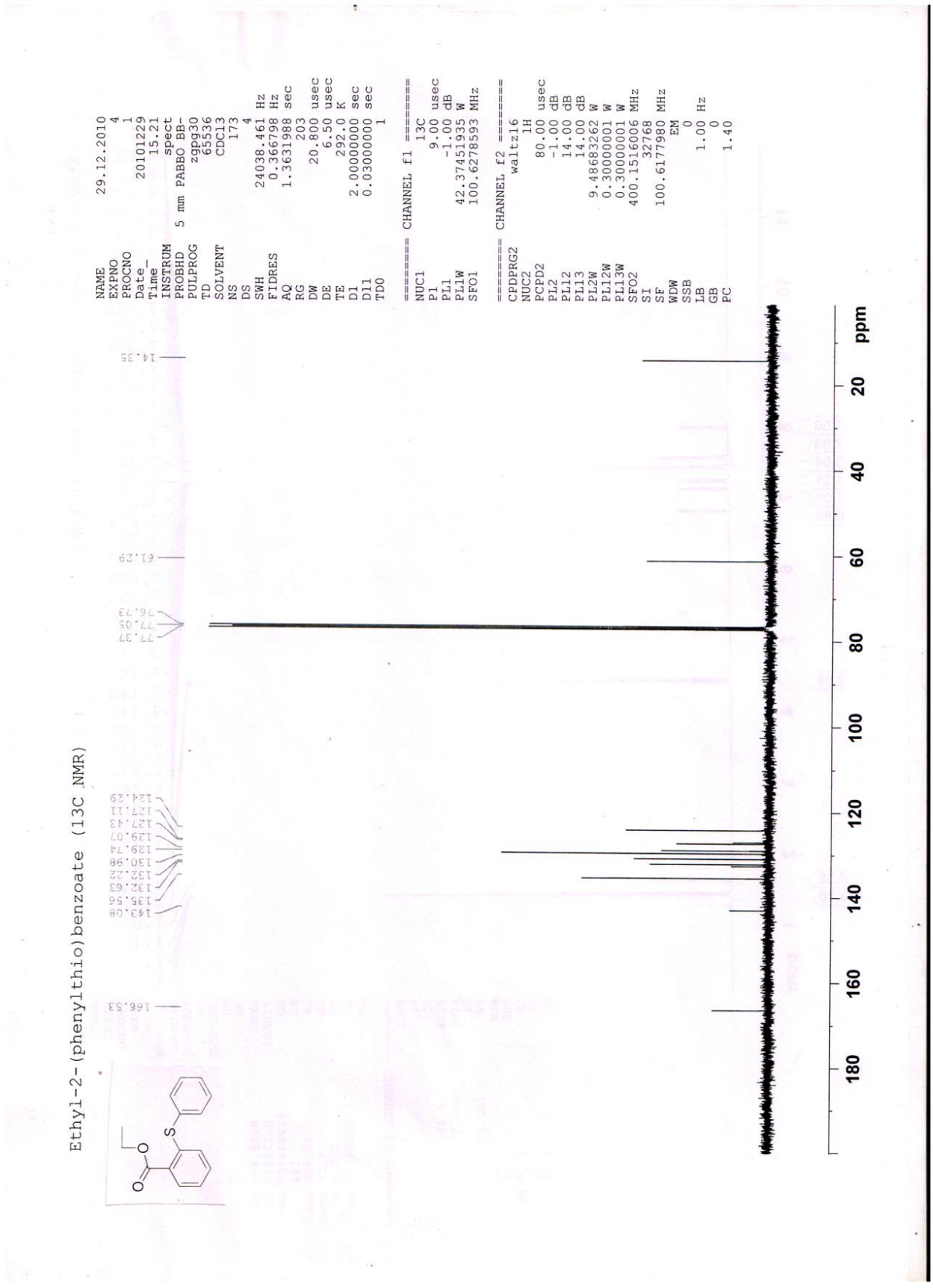
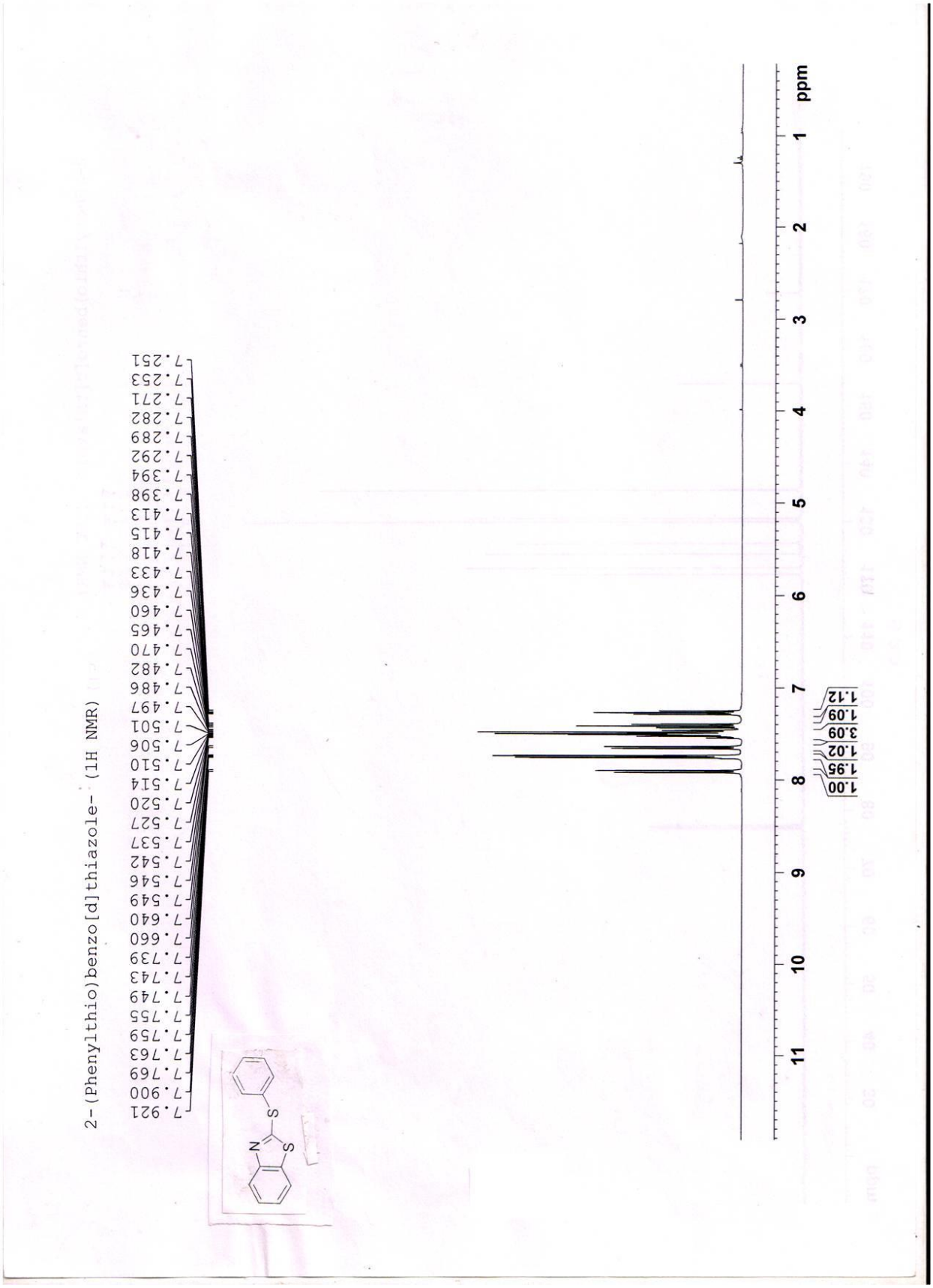
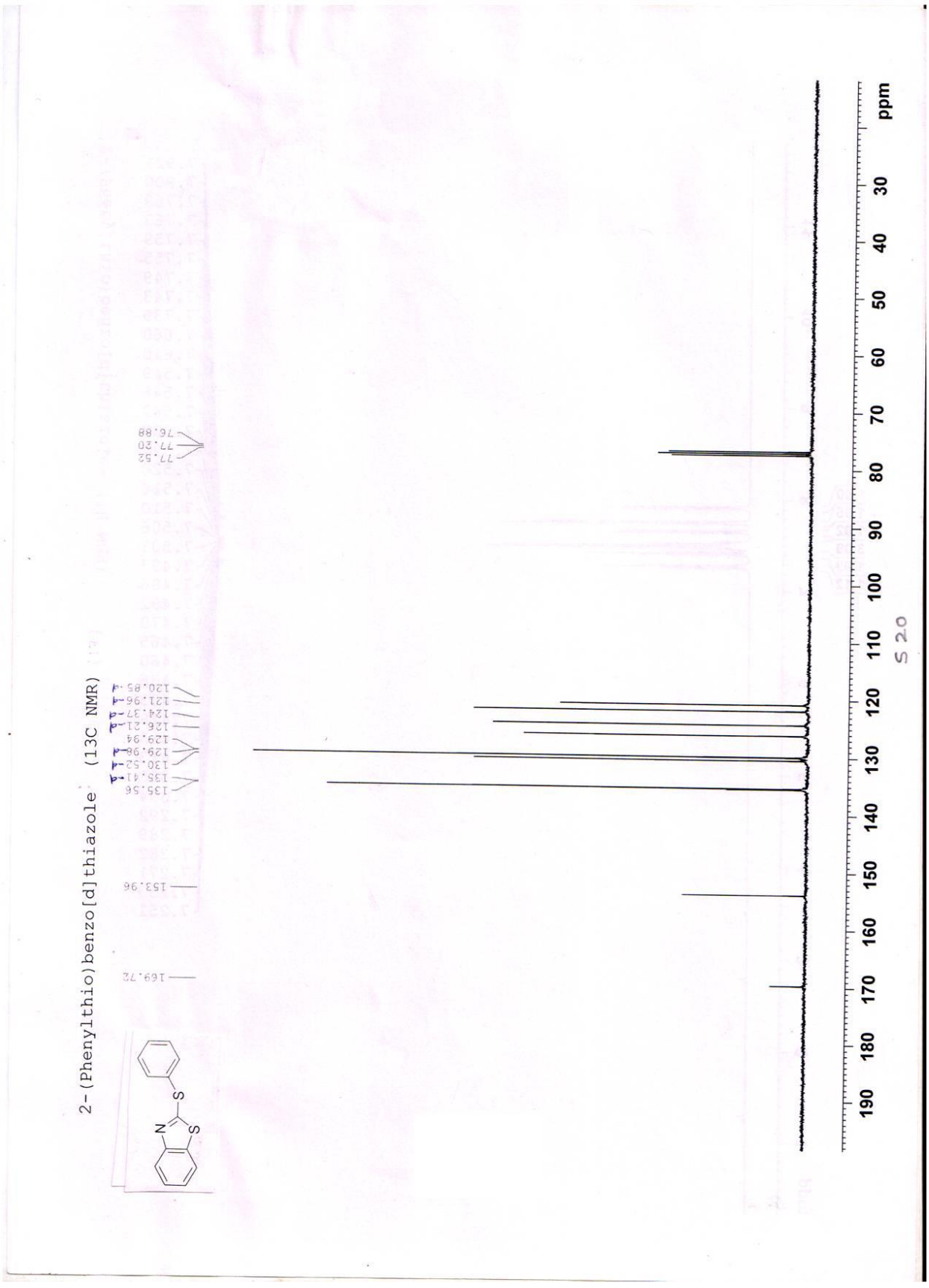
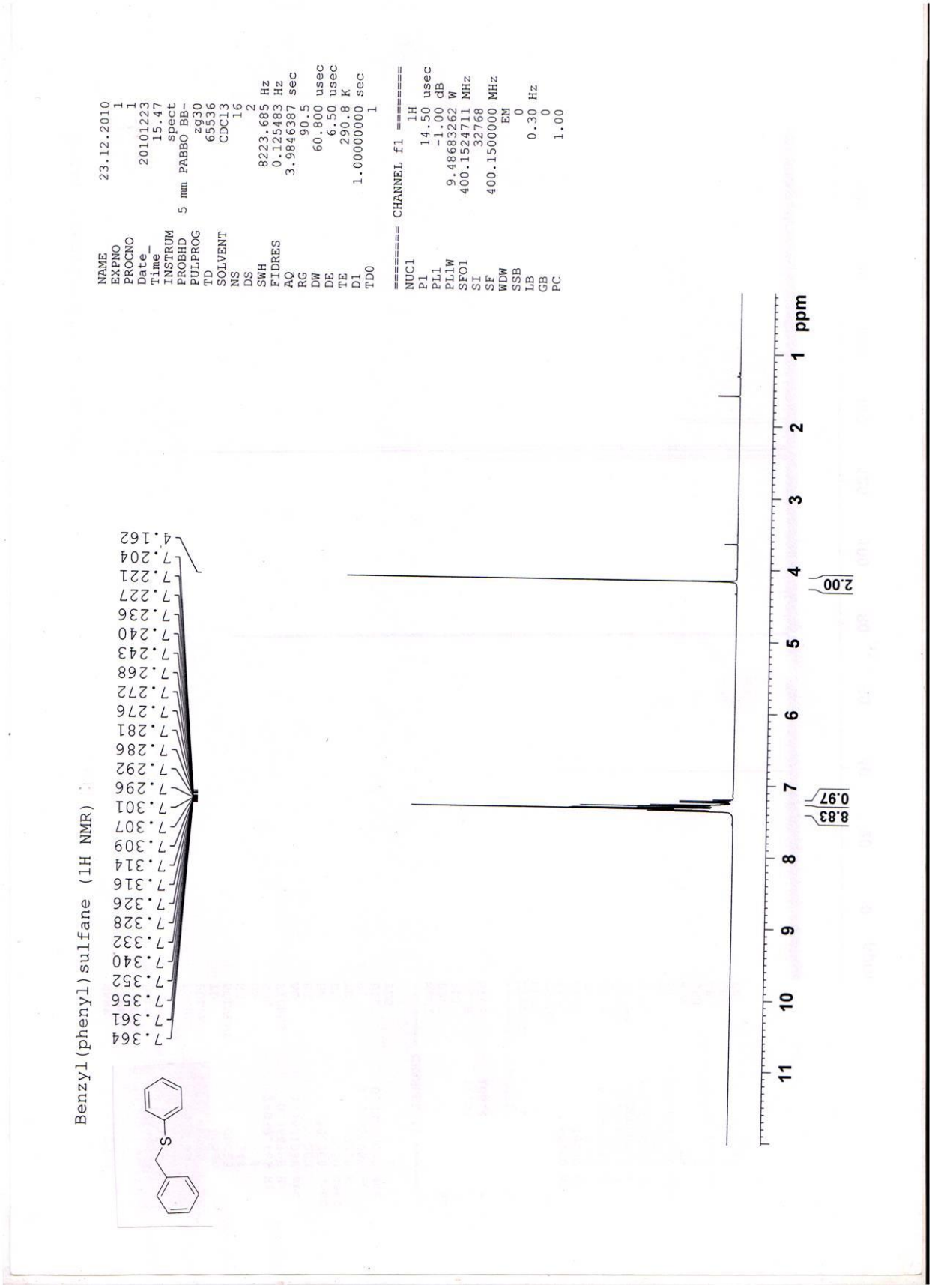
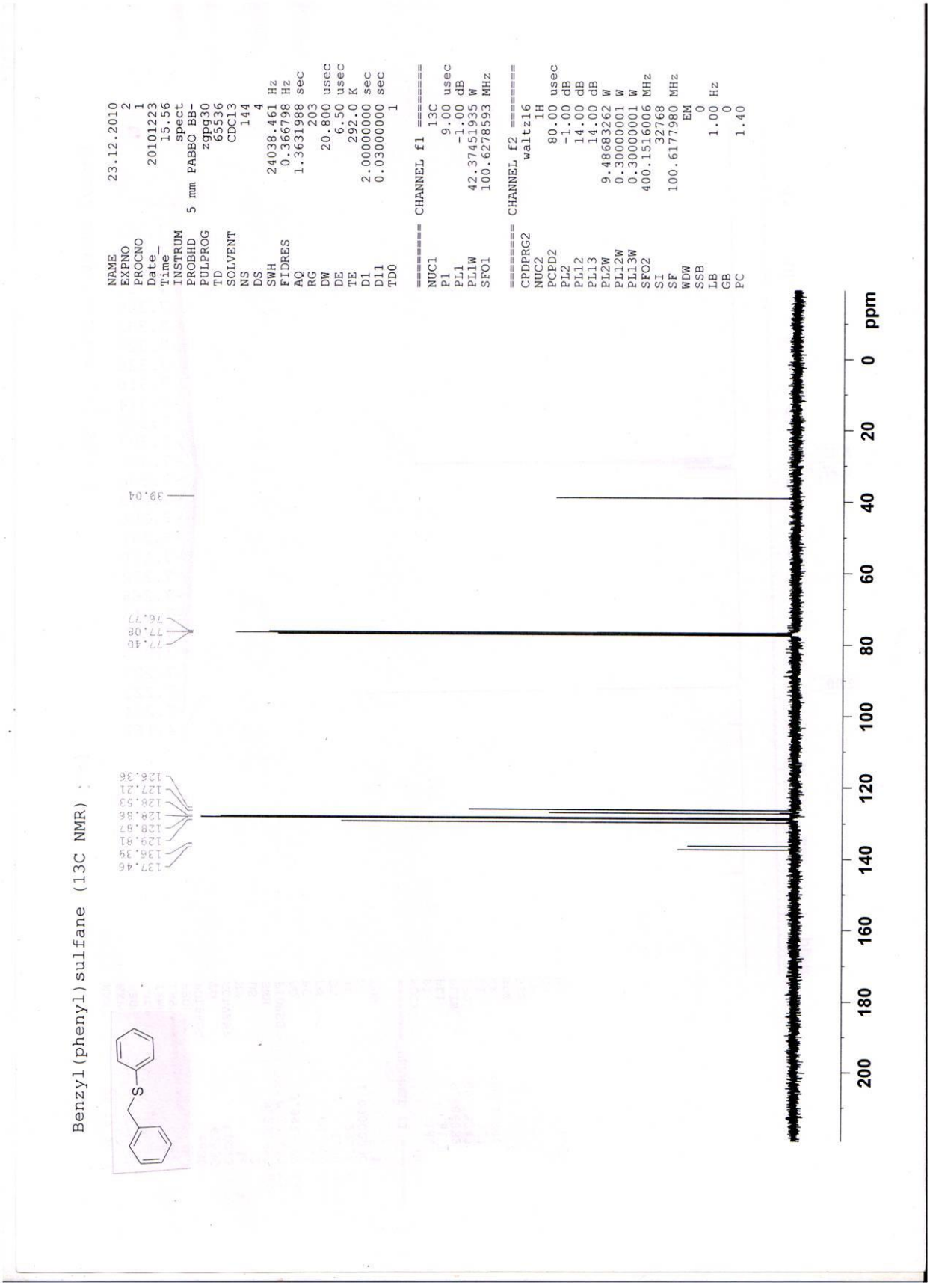
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 144
DW 60.800 usec
DE 6.50 usec
TE 290.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.50 usec
PL1 -1.00 dB
PL1W 9.48683262 W
SFO1 400.1524711 MHz
SI 32768
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.023
8.019
8.003
7.999
7.598
7.595
7.592
7.589
7.586
7.580
7.574
7.465
7.458
7.455
7.452
7.448
7.441
7.282
7.278
7.274
7.260
7.257
7.256
7.253
7.239
7.235
7.165
7.162
7.146
7.143
7.128
7.125
6.842
6.840
6.822
6.819
4.471
4.454
4.436
4.418
1.623
1.463
1.445
1.427
ppm
1.00
2.03
3.04
1.21
1.01
0.99
2.03
0.38
3.10

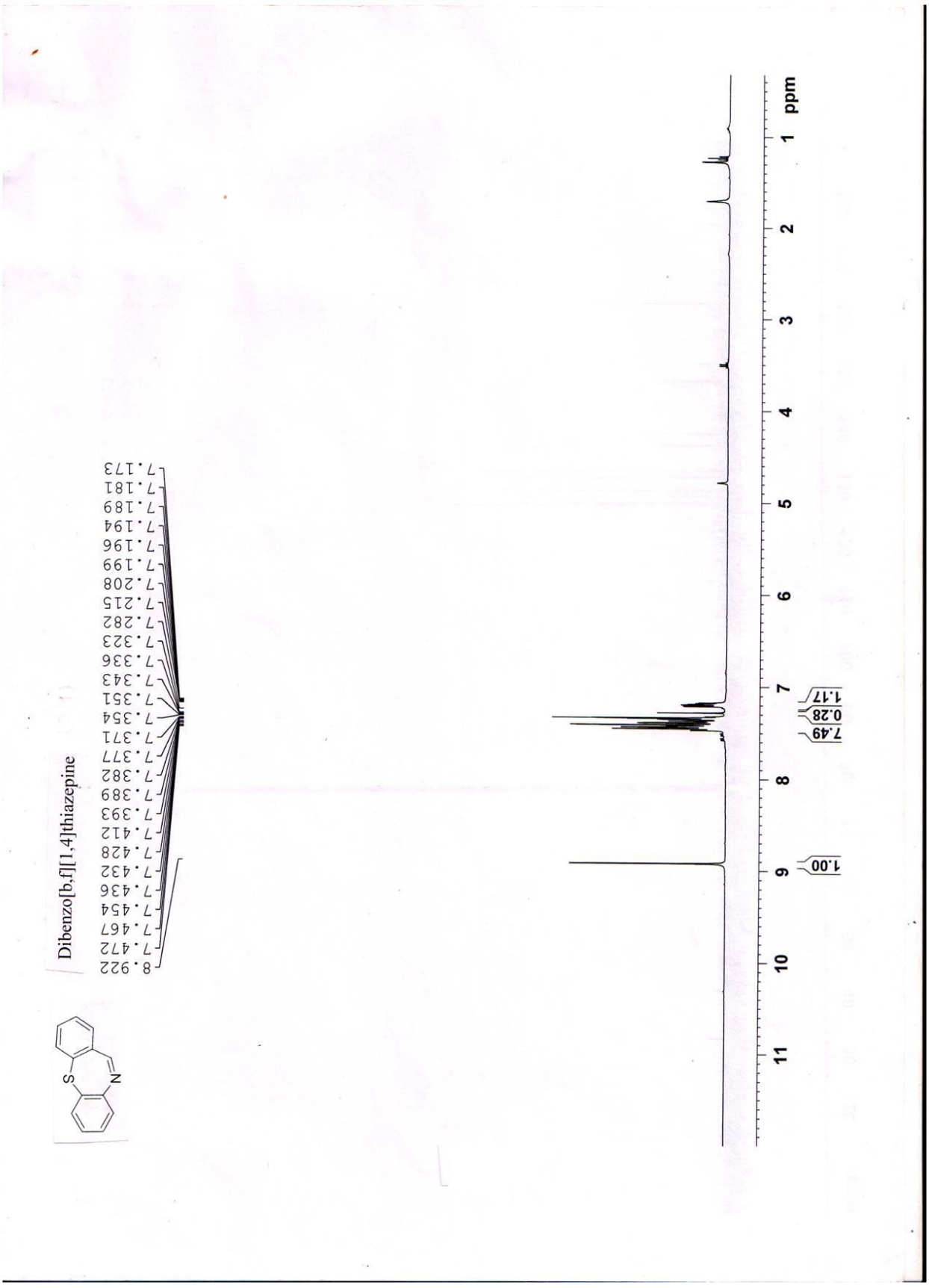

Ethyl-2-(phenylthio)benzoate (13C NMR)
166.53
143.08
135.56
132.63
132.22
130.98
129.74
129.07
127.43
127.11
124.29
77.37
77.05
76.73
61.29
14.35
NAME 29.12.2010
EXPNO 4
PROCNO 1
Date_ 20101229
Time_ 15.21
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 173
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 100.6278593 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
PL2W 9.48683262 W
PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 ppm


2-(Phenylthio)benzo[d]thiazole- (1H NMR)
7.921
7.900
7.769
7.763
7.759
7.755
7.749
7.743
7.739
7.660
7.649
7.640
7.549
7.546
7.542
7.537
7.527
7.520
7.514
7.510
7.506
7.501
7.497
7.486
7.482
7.470
7.465
7.460
7.436
7.433
7.418
7.415
7.413
7.398
7.394
7.292
7.289
7.282
7.271
7.253
7.251
1.00
1.95
1.02
3.09
1.09
1.12
ppm
1
2
3
4
5
6
7
8
9
10
11
S
N
S


2-(Phenylthio)benzo[d]thiazole (13C NMR)
169.72
153.96
135.56
135.41
130.52
129.98
129.94
126.21
124.37
121.96
120.85
77.52
77.20
76.88
S 2.0
ppm


Benzyl(phenyl)sulfane (1H NMR)
7.364
7.361
7.356
7.352
7.340
7.332
7.328
7.326
7.316
7.314
7.309
7.307
7.301
7.296
7.292
7.286
7.281
7.276
7.272
7.268
7.243
7.240
7.236
7.227
7.221
7.204
4.162
NAME
EXPNO
PROCNO
Date_
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT
NS
DS
SWH
FIDRES
AQ
RG
DW
DE
TE
D1
TD0
CHANNEL f1
NUC1
P1
PL1
PL1W
SFO1
SI
SF
WDW
SSB
LB
GB
PC
23.12.2010
20101223
15.47
spect
5 mm PABBO BB-
zg30
65536
CDC13
16
2
8223.685 Hz
0.125483 Hz
3.9846387 sec
90.5
60.800 usec
6.50 usec
290.8 K
1.00000000 sec
1
1H
14.50 usec
-1.00 dB
9.48683262 W
400.1524711 MHz
32768
400.1500000 MHz
EM
0
0.30 Hz
0
1.00
2.00
0.97
8.83
ppm


Benzyl(phenyl)sulfane (13C NMR)
NAME 23.12.2010
EXPNO 2
PROCNO 1
Date_ 20101223
Time_ 15.56
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 144
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 292.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 100.6278593 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.00 dB
PL13 14.00 dB
PL2W 9.48683262 W
PL12W 0.30000001 W
PL13W 0.30000001 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
39.04
77.40
77.08
76.77
137.46
136.39
129.81
128.87
128.86
128.53
127.21
126.36
200 180 160 140 120 100 80 60 40 20 0 ppm


Dibenzo[b,f][1,4]thiazepine
8.922
7.472
7.467
7.454
7.436
7.432
7.428
7.412
7.393
7.389
7.382
7.377
7.371
7.354
7.351
7.343
7.336
7.323
7.282
7.215
7.208
7.199
7.196
7.194
7.189
7.181
7.173
S
N
1.00
7.49
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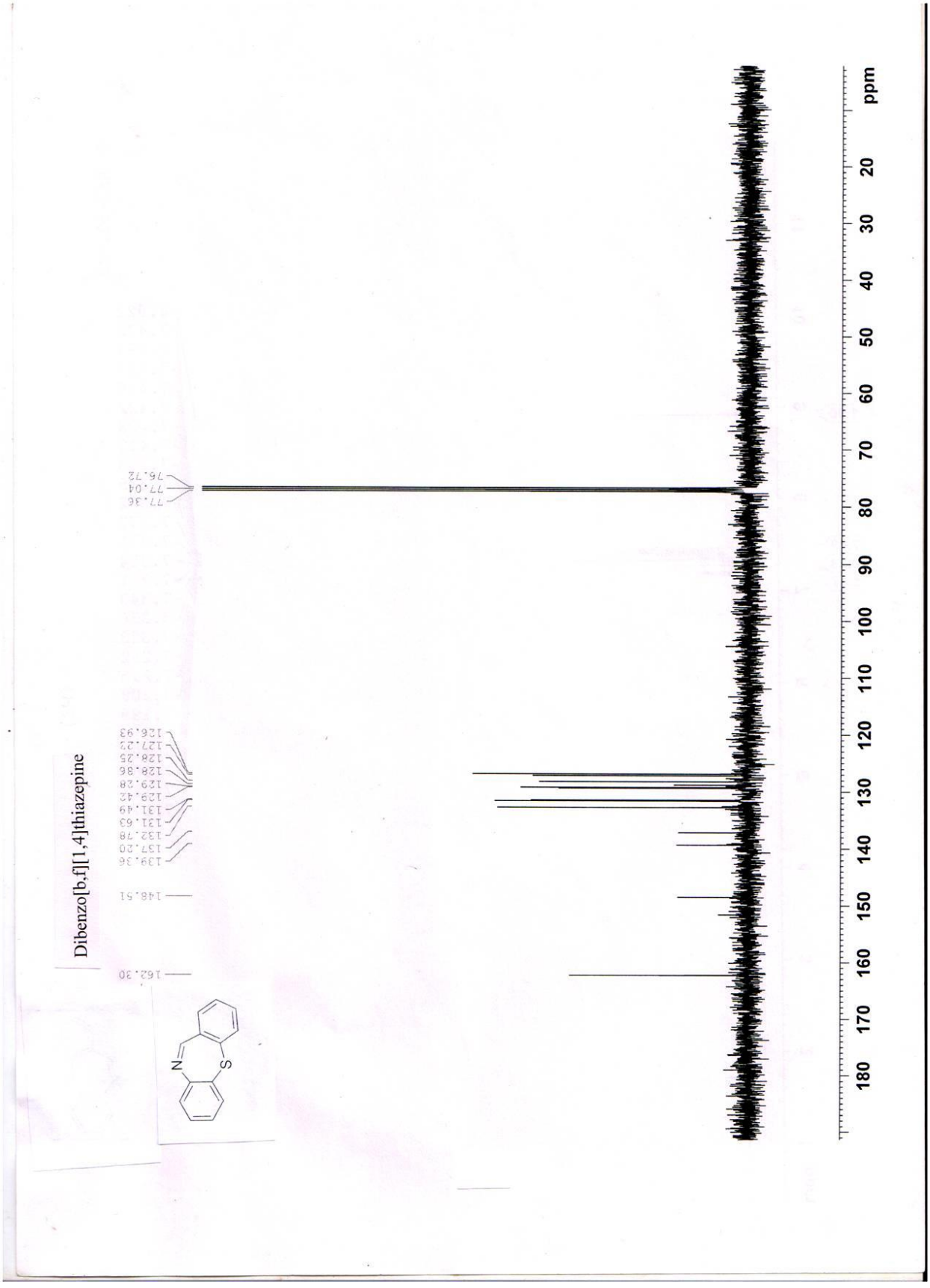
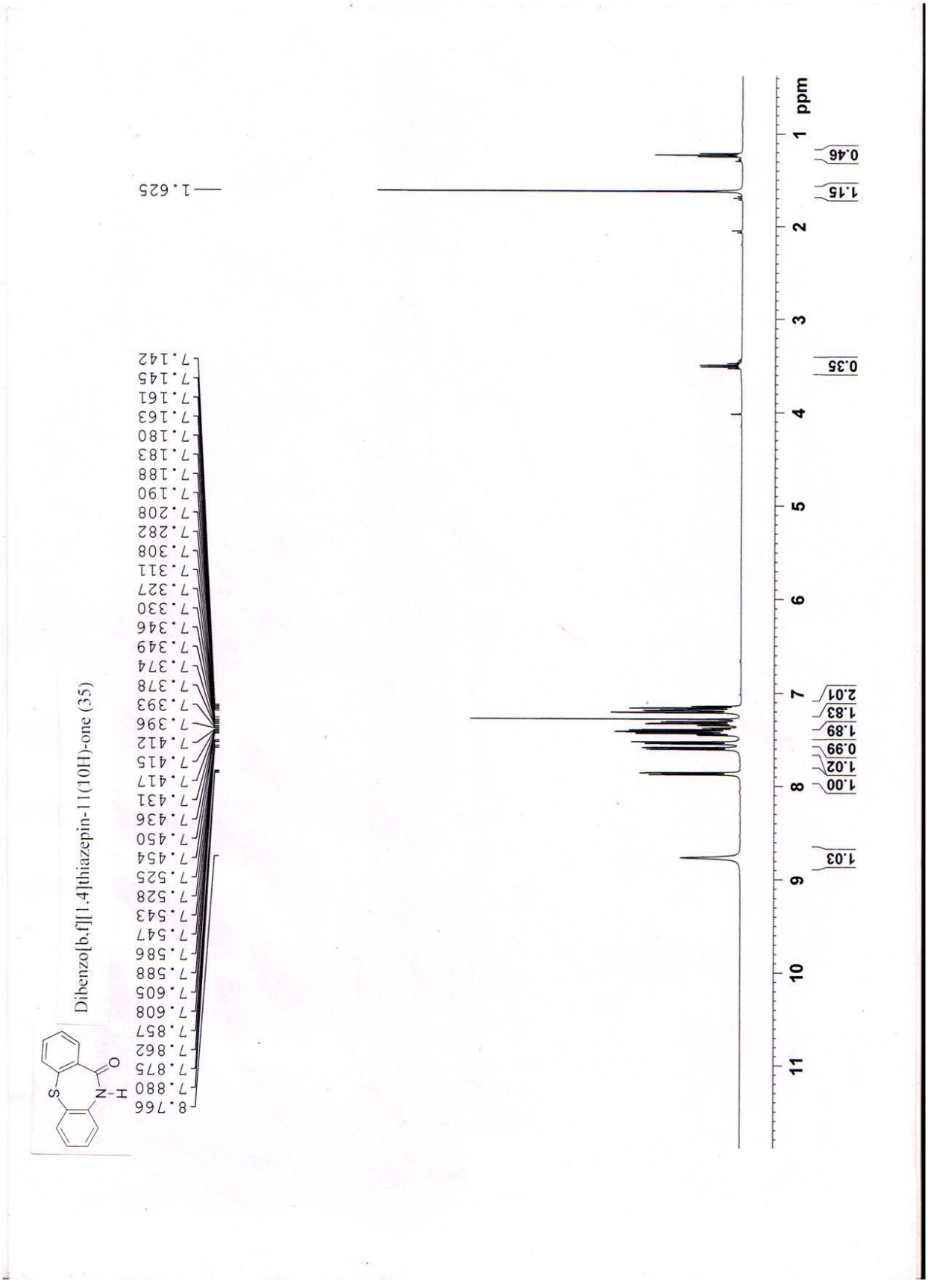
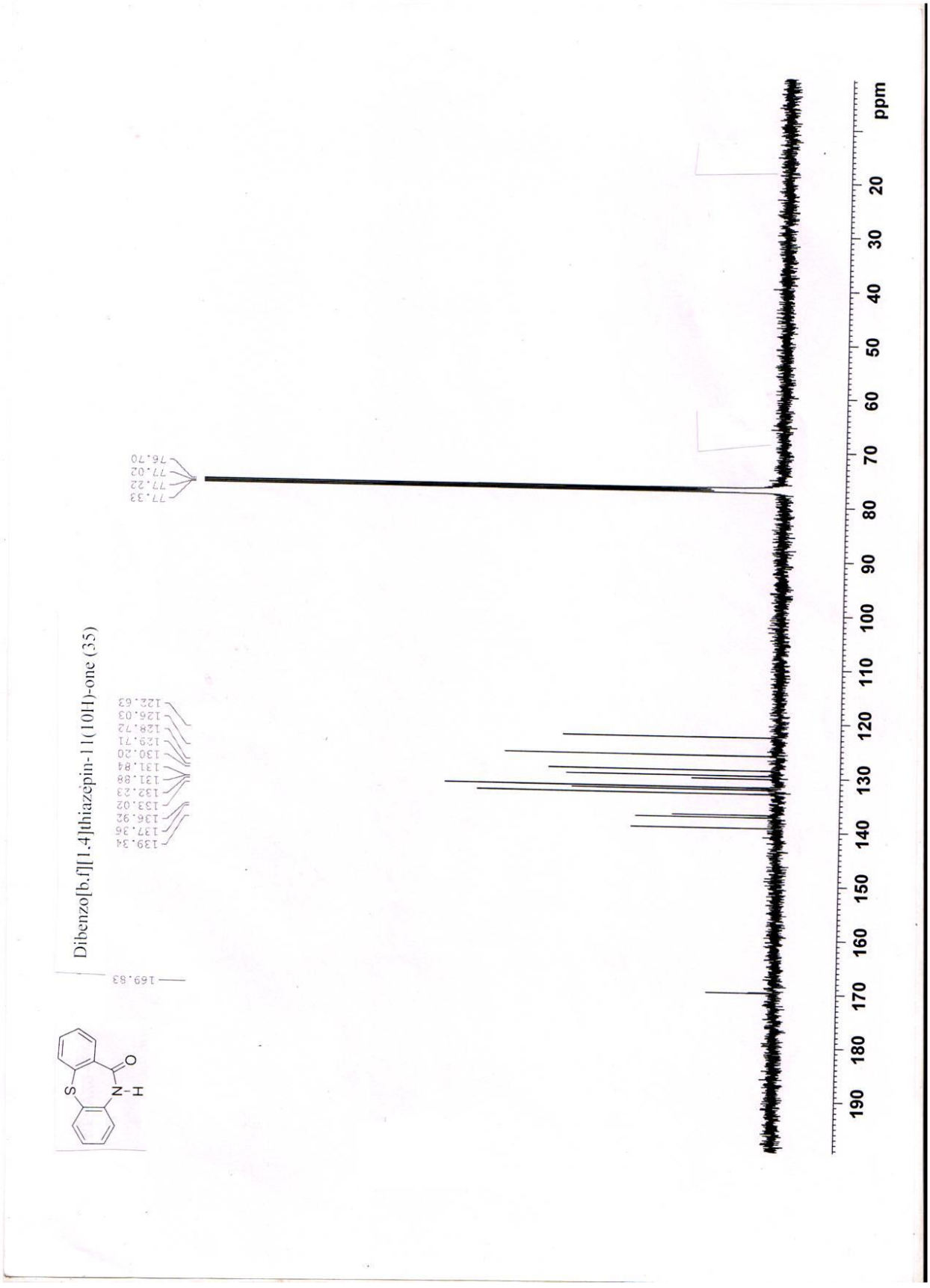
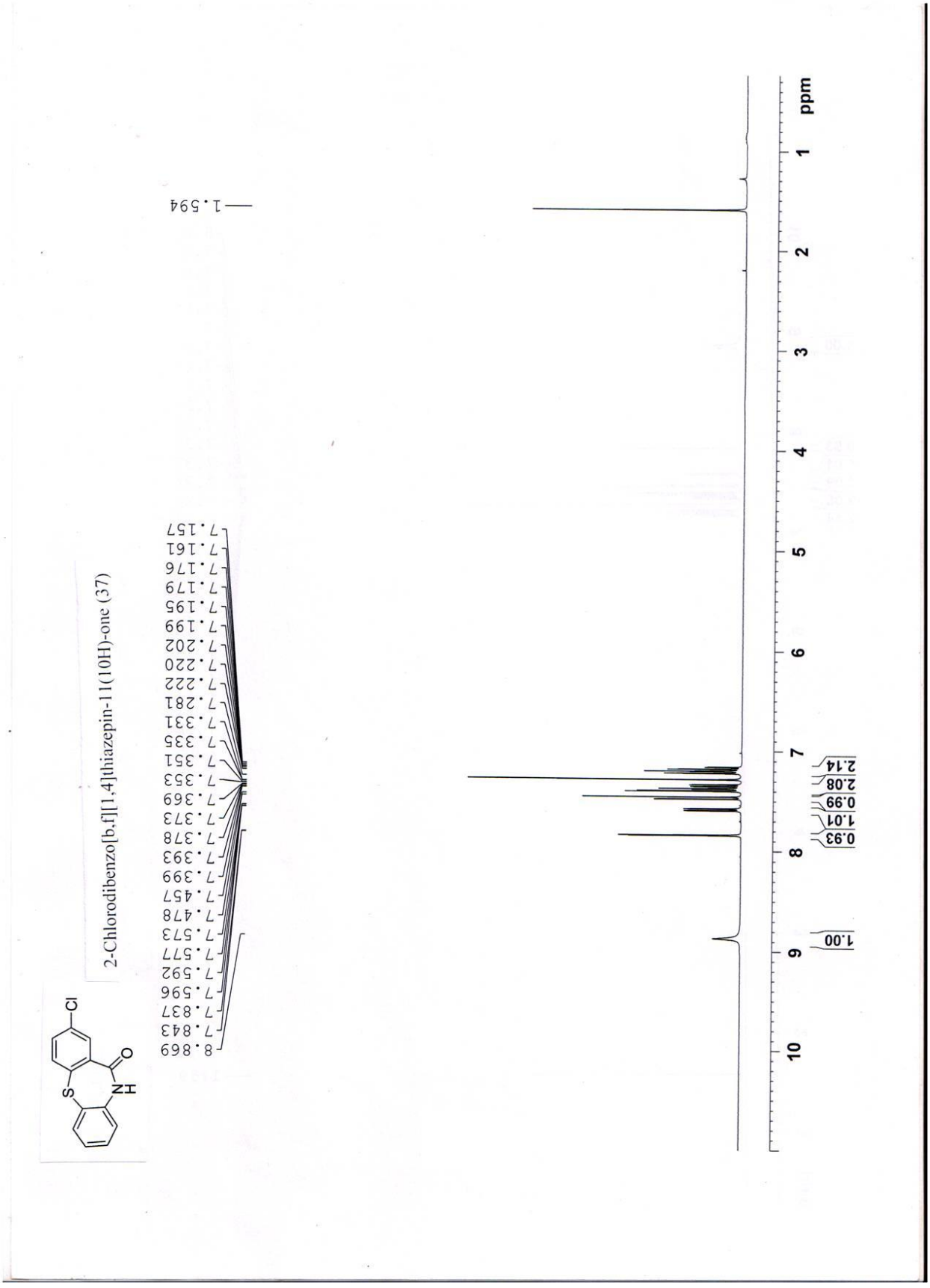
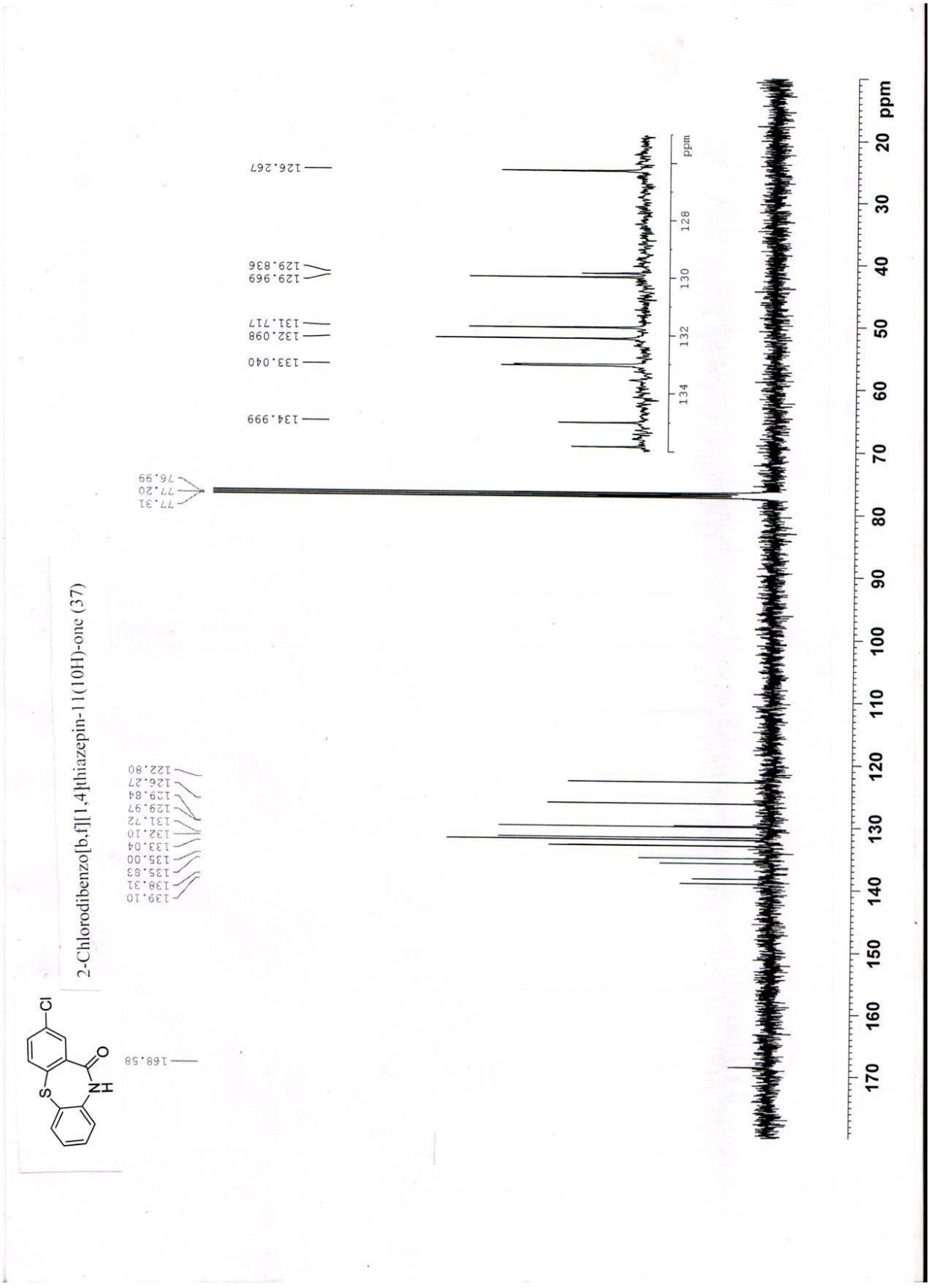
1.17
ppm


Dibenzo[b,f][1,4]thiazepine
162.30
148.51
139.36
137.20
132.78
131.63
131.49
129.42
129.28
128.86
128.25
127.27
126.93
77.36
77.04
76.72
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
N
S


Dibenzo[b,f][1,4]thiazepin-11(10H)-one (35)
1.625
7.142
7.145
7.161
7.163
7.180
7.183
7.188
7.190
7.208
7.282
7.308
7.311
7.327
7.330
7.346
7.349
7.374
7.378
7.393
7.396
7.412
7.415
7.417
7.431
7.436
7.450
7.454
7.525
7.528
7.543
7.547
7.586
7.588
7.605
7.608
7.857
7.862
7.875
7.880
8.766
ppm
0.46
1.15
0.35
2.01
1.83
1.89
0.99
1.02
1.00
1.03


Dibenzo[b,f][1,4]thiazepin-11(10H)-one (35)
169.83
139.34
137.35
136.92
133.02
132.23
131.88
131.84
130.20
129.71
128.72
126.03
122.63
77.33
77.22
77.02
76.70
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
O
S
N-H


2-Chlorodibenzo[b,f][1,4]thiazepin-11(10H)-one (37)
Cl
O
N
H
S
8.869
7.843
7.837
7.596
7.592
7.577
7.573
7.478
7.457
7.399
7.393
7.378
7.373
7.369
7.353
7.351
7.335
7.331
7.281
7.222
7.220
7.202
7.199
7.195
7.179
7.176
7.161
7.157
1.594
ppm
1 2 3 4 5 6 7 8 9 10
1.00
0.93
1.01
0.99
2.08
2.14


2-Chlorodibenzo[b,f][1,4]thiazepin-11(10H)-one (37)
Cl
S
N
H
O
168.58
139.10
138.31
135.83
135.00
133.04
132.10
131.72
129.97
129.84
126.27
122.80
77.31
77.20
76.99
134.999
133.040
132.098
131.717
129.969
129.836
126.267
ppm
128
130
132
134
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

Chapter 5

Iron-catalyzed regioselective synthesis of substituted pyrazoles

5.1. Introduction

The presence of the pyrazole motif in several blockbuster drugs and pesticides including sildenafil (Viagra), celecoxib (Celebrex), rimonabant (Acomplia), Fipronil, Pyraclonil, Apixaban and Pyracolfos (Figure 1) made this heterocycle a popular synthetic target for pharmaceutical and agrochemical industries.[1] Furthermore, substituted pyrazoles are privileged structural units in many functional materials including optical brightners,[2] UV stabilizers,[3] photoinduced electron transfer systems[4] etc. These are also used in supramolecular chemistry,[5] as pluripotent ligands in coordination chemistry,[6] as building blocks in heterocycle synthesis, while some have liquid crystalline properties.[7]

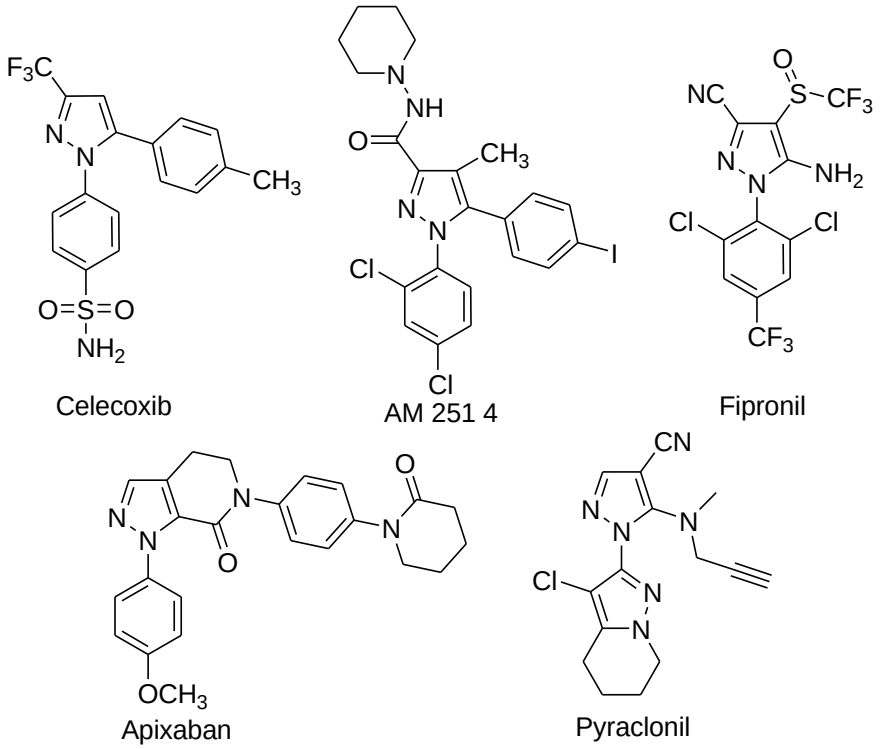
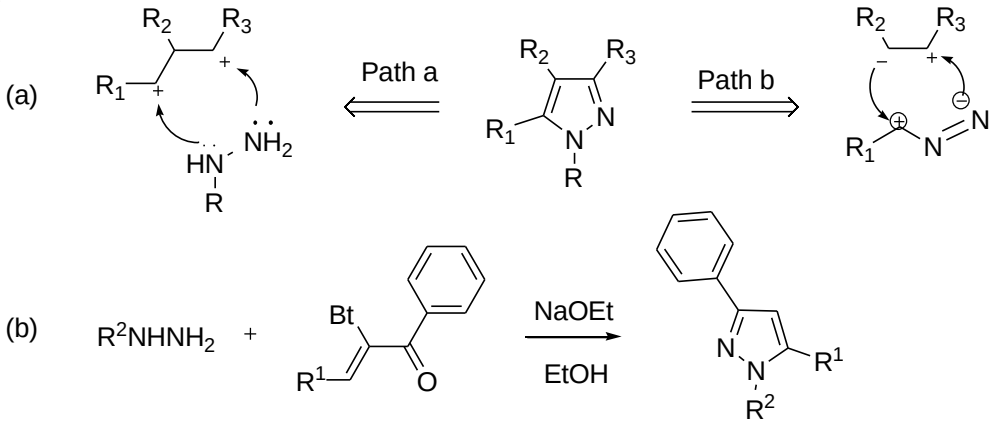


Figure 1. Pyrazole containing medicinal compounds

Due to the wide spread importance of pyrazole derivatives, new and complementary methods have been developed for their synthesis. Conventional approach involves the condensation of hydrazines with 1,3-dicarbonyl compounds[8] or their 1,3-dielectrophilic equivalents (Scheme 1a, path a). However, the multistep access of appropriately functionalized 1,3-dicarbonyl compounds and the formation of regioisomeric mixtures are the inevitable drawbacks of the above method.[9] The replacement of 1,3-dicarbonyl compounds with acetylenic

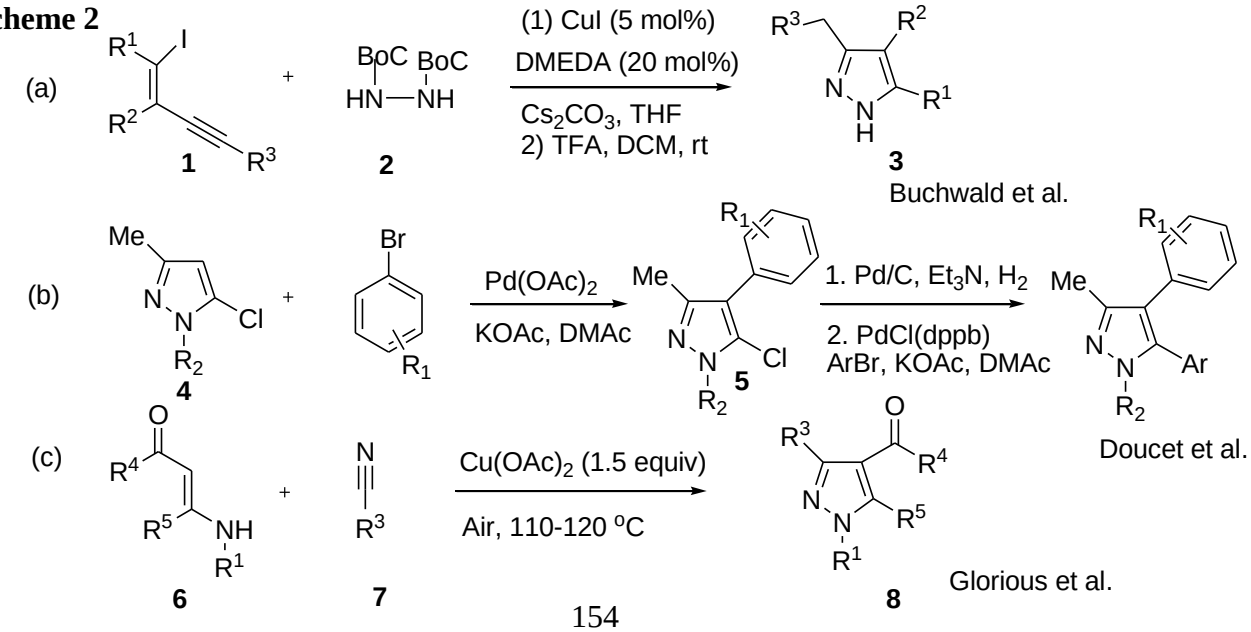
or olefinic ketones somewhat improves the selectivity of the synthesis. For instance, Katritzky et al. employed α-benzotriazolyl-α, β-unsaturated ketones for the regioselective synthesis of 1,3,5-triaryl-4-alkyl pyrazoles by reacting with hydrazine derivatives (Scheme 1b).[10] To improve the regioselectivity, 1,3-dipolar cycloaddition of 1,3-dipoles to dipolarophiles have been emerged as a complementary approach (Scheme 1a, path b).[11]

Scheme 1



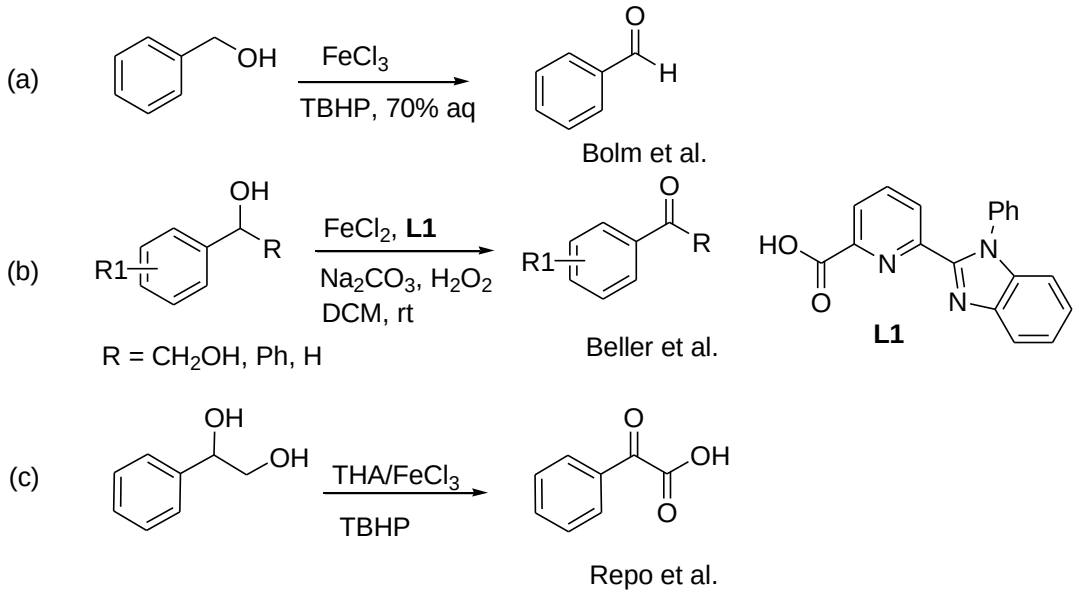
Moreover, in the above method (path b) the question of regioselectivity is transferred to the preparation and handling of 1,3-dipoles.[11g] During the last decade, transition-metal-mediated C-N and C-C cross-coupling methodology have been developed with the aim to increase the regioselectivity in the synthesis of substituted pyrazoles.[12] In this regard, Buchwald et al. reported the synthesis of substituted pyrazoles **3** by Cu-mediated cross-coupling between vinyl iodides **1** with hydrazine derivatives **2** in THF (Scheme 2a).[13]

Scheme 2



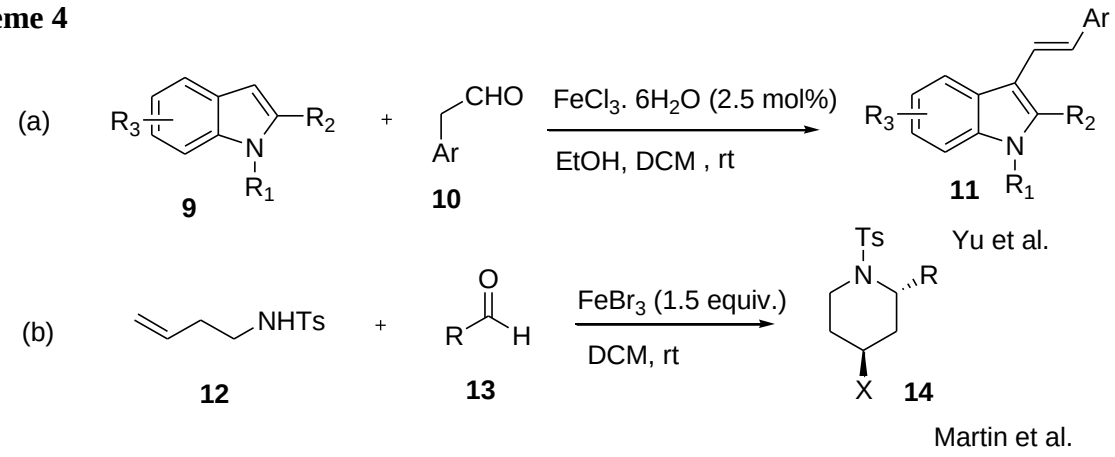
Recently, the group of Doucet demonstrated the Pd-mediated regioselective synthesis of 4-aryl pyrazoles **5** by coupling **4** with aryl bromides using chloro as a directing group. In subsequent steps, further arylation at C_5 position occurred by Pd-mediated deprotection and C-C coupling reactions between **5** with aryl bromides (Scheme 2b).[14] Recently, the group of Glorious developed copper-promoted oxidative N-N bond formation strategy for the synthesis of tetrasubstituted pyrazoles **8** from enamines **6** and nitriles **7** (Scheme 2c).[15] But the above method required excess of nitriles and stoichiometric amounts of copper(**II**) acetate. Later, the same group simplified their methodology by adding 2-picolinic acids as the additive and carrying out the reaction using catalytic amount of $Cu(OAc)_2$ in DMF.[16] However, these methods utilized expensive and toxic metals and often followed a number of steps for the synthesis of target compounds. Thus, development of efficient, less expensive, and environmental friendly catalysts have been found to be attractive for regioselective synthesis of pyrazoles. On the other hand, iron catalyzed reactions are paramount interest in recent years due to the low cost, wide abundance and less toxic nature.[17] Hence forth iron-mediated Friedel−Crafts reactions,[18] aldol condensation reactions,[19] carbometalation reactions,[20] and cycloaddition reactions[21] have been reported. Iron catalysts are also successfully employed for the oxidation of alcohols to the corresponding carbonyl compounds in presence of peroxide as an oxidant. For example, Bolm et al. described Fe-mediated oxidation of benzylic alcohol in presence of TBHP (Scheme 3a).[22]

Scheme 3



Beller et al. described a convenient and selective oxidation of benzylic and allylic alcohols in presence of **L1** and hydrogen pereoxide at room temperature (Scheme 3b).[23] Repo and co-workers reported Fe-mediated oxidation of diols in presence of thiamyl acetate and TBHP (Scheme 3c).[24] Liang and co-workers utilized the iron chloride and TEMPO derivatives for the oxidation of primary alcohols.[23b] In addition to the oxidizing ability of Fe catalysts, the lewis acid behavior of Fe catalysts activate the carbonyl carbon. This often facilitates the formation of C-C and C-N bond. For instance, Yu et al. reported iron-mediated C-C bond forming reactions between **9** and **10** by activating the aldehyde derivatives **10** (Scheme 4a).[25] Martin et al. demonstrated iron-catalyzed C-N bond formation strategy towards the synthesis of **14** by reacting N-tosylamine derivatives **12** with aldehydes **13** (Scheme 4b).[26]

Scheme 4



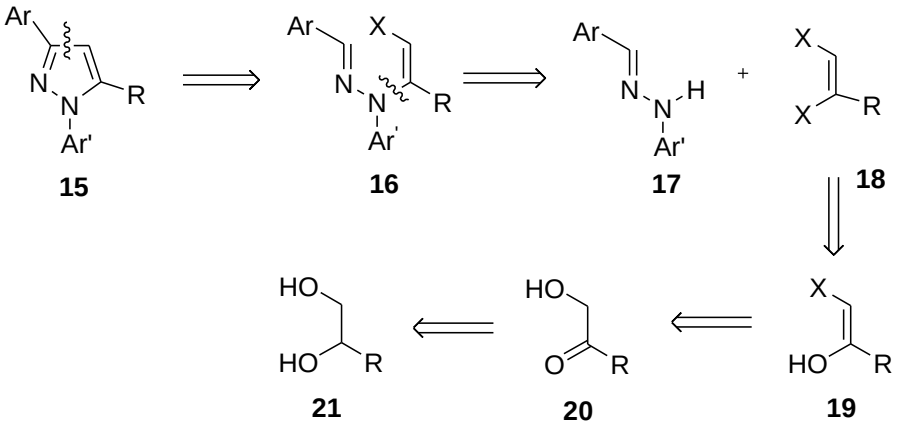
Considering the role of Fe catalysts in oxidation process as well as coordination property of Fe catalysts as Lewis acid for C=O activation, we deemed that simple vicinal diols may be used as a coupling partner for the synthesis of heterocycles. For the synthesis of highly important nitrogen containing molecules like pyrazoles, hydrazones can be used as another coupling partner. With this in our mind, we explore a new operationally simple catalytic method for the regioselective synthesis of substituted pyrazoles.

5.2. Results and Discussion

Our strategy toward the synthesis of substituted pyrazoles is outlined in Scheme 5. This involves the condensation of α-hydroxy carbonyl compounds **20** with diarylhydrazones **17** to give **16**; the latter may undergo transition-metal-catalyzed reductive coupling to afford the desired pyrazoles **15**. We envisioned that the intermediate α-hydroxy carbonyl compounds **20**

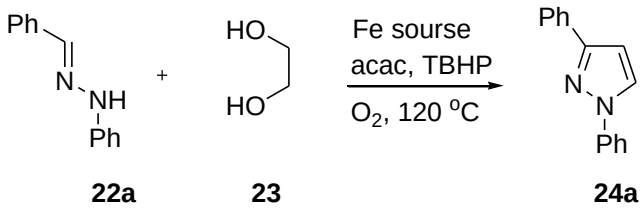
can be achieved in situ by the oxidation of vicinal diols **21**. Indeed, our anticipation to access **20** from **21** is based on the pioneering work of Bolm,[22] Beller,[23] and Repo[24] as described earlier.

Scheme 5



To test the viability of our strategy, we took diphenylhydrazone and ethylene glycol as model substrate (Scheme 6).

Scheme 6



To find a suitable reaction conditions, screening experiments were performed by subjecting different combinations of iron sources, ligands and solvents at different temperature and the results were summarized in Table 1. When the reaction was carried out in presence of $FeCl_3$, TBHP and pyridine, no desired product was formed even at elevated temperature (120 °C). On the other hand, the reactions of hydrazone **22a** with 5 mol % of $FeCl_3$ and 2 equiv of ethyl acetoacetate afford pyrazole **24a** in 13 % yield (Table 1, entry 1). The formation of **24a** was evident from the spectral data. For example, the presence of molecular ion peak at m/z 221 ($[M+H]^+$ $C_{15}H_{12}N_2$) in the mass spectrum and the appearance of the doublet at 6.79 with J = 2.4 Hz confirmed the formation of **24a**. The product formation **24a** was further confirmed from 11 line signals in ^{13}C NMR spectrum. When the same reaction was carried out using TMEDA as the ligand no product formation was observed (Table 1, entry 3)

Table 1. Optimization of reactions between diphenyl hydrazones and ethylene glycol

Entry	Catalyst	Ligand	Yield (%)
1	$FeCl_3$	EAA	13
2	$FeCl_3$	DMEDA	10
3	$FeCl_3$	TMEDA	00
4	$FeCl_3$	1,10-phen	00
5	$FeCl_3$	DEM	≤5
6	$FeCl_3$	acac	75
7	___	acac	00
8	$FeCl_3$	___	13
9	$FeCl_2.2H_2O$	acac	40
10	$Fe(acac)_3$	acac	≤5
11	Fe_3O_4	acac	20

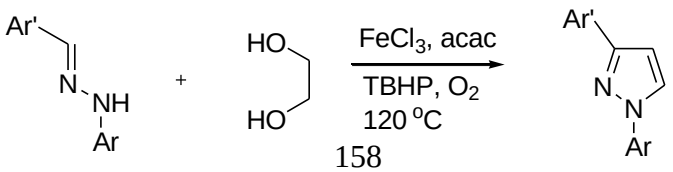
Reaction conditions: diphenylhydrazone (100 mg, 0.51 mmol), ethylene glycol (2 mL), catalyst (5 mol %), ligand (1 mmol), TBHP (0.51 mmol), heated at 120 °C, 6 h, O_2 balloon.

Notably, by applying acetyl acetone as the ligand, the yield of **24a** was significantly increased to 75 %. The reaction became sluggish in N_2 as well as in air and led to **24a** in 10 % and 25 % yield, respectively, whereas under O_2 atmosphere reaction proceeds rapidly and resulted **24a** in 75 % yield. When we carried out the reaction in absence of TBHP or $FeCl_3$, no product was formed. This result confirmed the significant role of iron for the synthesis of substituted pyrazoles. Thus, an optimum yield of **24a** was obtained when diphenylhydrazone **22a** and ethylene glycol were heated at 120 °C in the presence of 5 mol % of $FeCl_3$, 2 equiv of acac, and 1 equiv of TBHP under O_2 atmosphere.

Substrate Scope

We then turned our attention for the synthesis of a variety of 1,3-disubstituted pyrazoles containing both electron-donating and -withdrawing aryl substituents (Scheme 7).

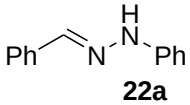
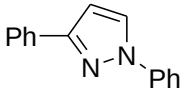
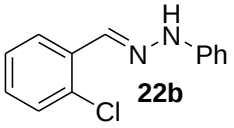
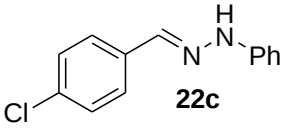
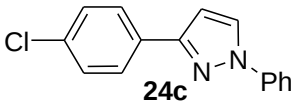
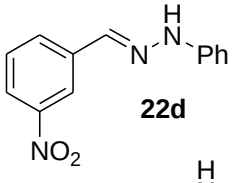
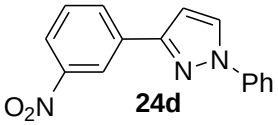
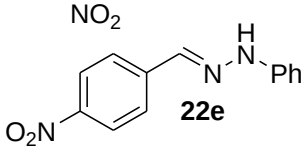
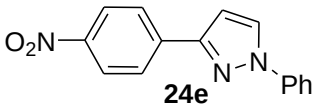
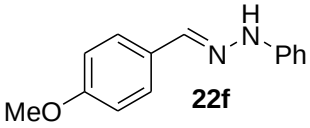
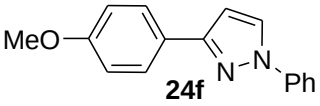
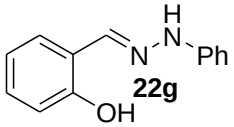
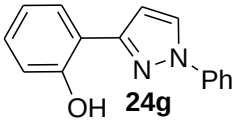
Scheme 7



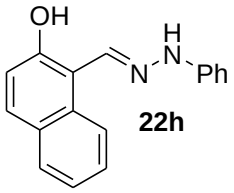
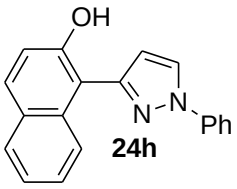
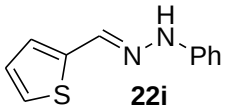
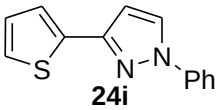
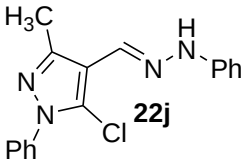
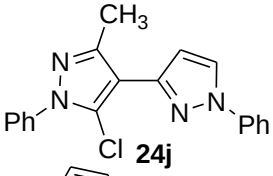
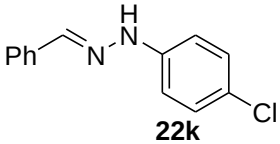
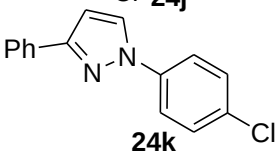
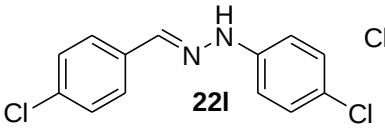
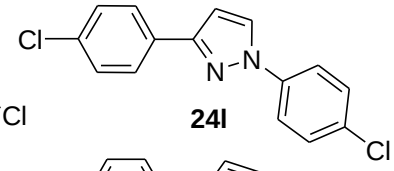
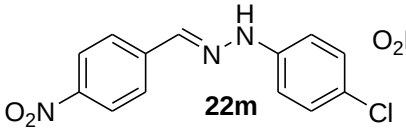
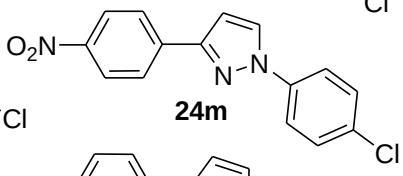
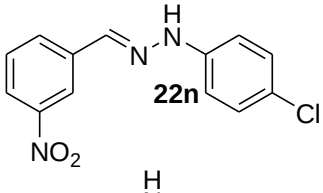
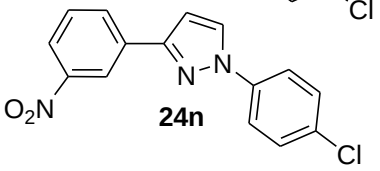
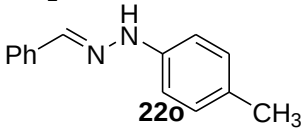
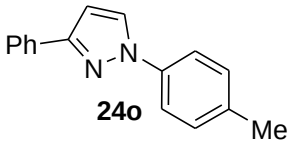
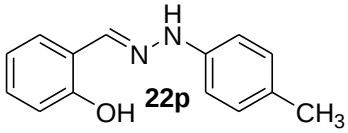
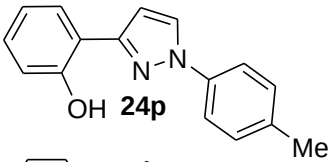
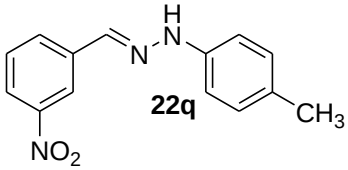
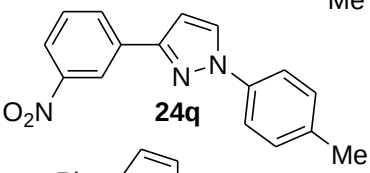
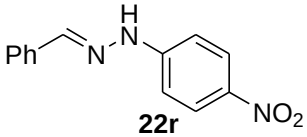
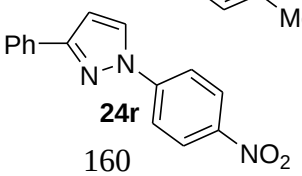
For example, when **22b** was reacted with ethylene glycol under optimum conditions, the product **24b** was obtained in good yield (Table 2, entry 2). Similarly other aryl hydrazones containing strong withdrawing groups like nitro, chloro resulted good yield of the 1,3-disustituted pyrazole product (Table 2, entries 3-5)

Our optimization condition was also applied to diarylhydrazones containing electron releasing groups like hydroxy and methoxy. Thus, reactions of compound **22f** with ethylene glycol afforded the product **24f** in 70 % yield (Table 2, entry 6). Interestingly, using our standard reaction conditions we were successfully synthesized heteroaromatic substituted pyrazoles. For instance, treatment of **22i** with ethylene glycol resulted **24i** in good yield (Table 2, entry 9).

Table 2. Synthesis of 1,3-disubstituted pyrazoles

Entry	Hydrazone	Pyrazole	Yield (%)
1	 **22a**	 **24a**	75
2	 **22b**	 **24b**	62
3	 **22c**	 **24c**	68
4	 **22d**	 **24d**	62
5	 **22e**	 **24e**	73
6	 **22f**	 **24f**	70
7	 **22g**	 **24g**	63

Continued ...

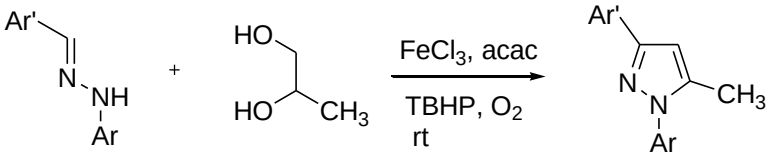
Entry	Hydrazone	Pyrazole	Yield (%)
8	 **22h**	 **24h**	65
9	 **22i**	 **24i**	68
10	 **22j**	 **24j**	65
11	 **22k**	 **24k**	77
12	 **22l**	 **24l**	85
13	 **22m**	 **24m**	71
14	 **22n**	 **24n**	74
15	 **22o**	 **24o**	61
16	 **22p**	 **24p**	58
17	 **22q**	 **24q**	60
18	 **22r**	 **24r**	00

Reaction conditions: diarylhydrazone (100 mg), ethylene glycol (2 mL), anhyd $FeCl_3$ (5 mol %), acac (2 equiv), TBHP (1 equiv), 6 h, O_2 balloon.

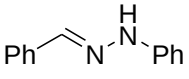
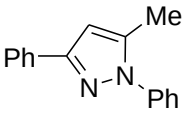
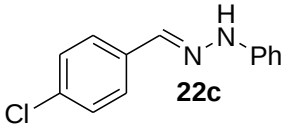
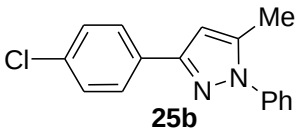
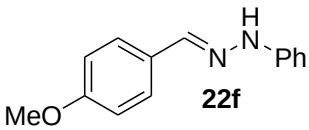
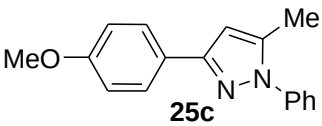
The presence of electron-donating substituents to the N-aryl group increases the reactivity of the hydrazone by increasing the nucleophilicity of the nitrogen, and hence, the reaction completed at lower temperature. For example, when **22o** reacted with ethylene glycol, the reaction was occurred at 90 °C. However, the presence of electron-withdrawing groups such as $-NO_2$ to the N-phenyl ring retards the reaction and the desired pyrazole was not formed even at elevated temperature (Table 2, entry 18).

With the optimized conditions, we then extend our protocol for the regioselective synthesis of 1,3,5-trisubstituted pyrazoles. Thus, the reaction of diarylhydrazones with 1,2-propanediol resulted 1,3,5-substituted pyrazoles in moderate to good yield (Table 3). Interestingly, these reactions proceed at room temperature in absence of any solvent, although an excess of diol was required.

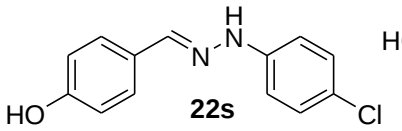
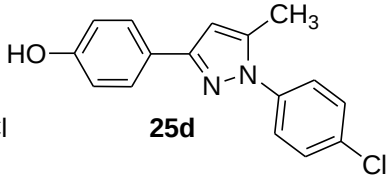
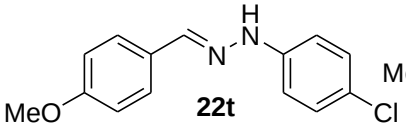
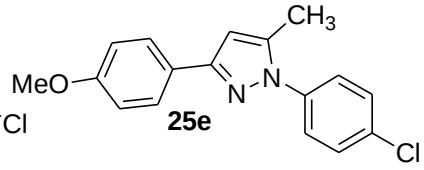
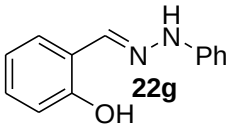
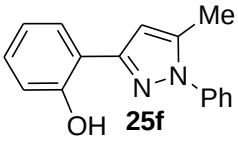
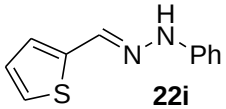
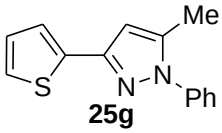
Table 3. Synthesis of 1,3,5-trisubstituted pyrazoles



22 **25**

Entry	Hydrazone	Pyrazole	Yield (%)
1	 **22a**	 **25a**	55
2	 **22c**	 **25b**	52
3	 **22f**	 **25c**	58

Continued…

Entry	Hydrazone	Pyrazole	Yield (%)
4	 **22s**	 **25d**	52
5	 **22t**	 **25e**	56
6	 **22g**	 **25f**	51
7	 **22i**	 **25g**	60

Reaction conditions: diarylhydrazone (100 mg), 1,2-propanediol (2 mL), anhyd $FeCl_3$ (5 mol %), acac (2 equiv), TBHP (1 equiv), 1 h, O_2 balloon.

When diphenylhydrazone **22a** reacted with 1,2-propanediol, 5-methyl-1,3-diphenyl-1H-pyrazole **25a** was formed regioselectively (Table 3, entry 1). The synthesis of **25a** was confirmed by the appearance of ^{1}H NMR signal at δ 6.55 (s, 1H) and 2.41 (s, 3H) along with 12 lines in ^{13}C NMR spectrum. A variety of 1,3,5-trisubstituted pyrazoles including both electron-donating and –withdrawing aryl groups were synthesized by reacting diarylhydrazones with 1,2-propanediol. The heteroaromatic substituted pyrazole **25g** can be prepared by reacting **22i** with 1,2-propanediol. Formation of the product **25g** was confirmed by the ^{1}H NMR signal at 6.45 (s, 1H) and 2.37 (s, 3H).

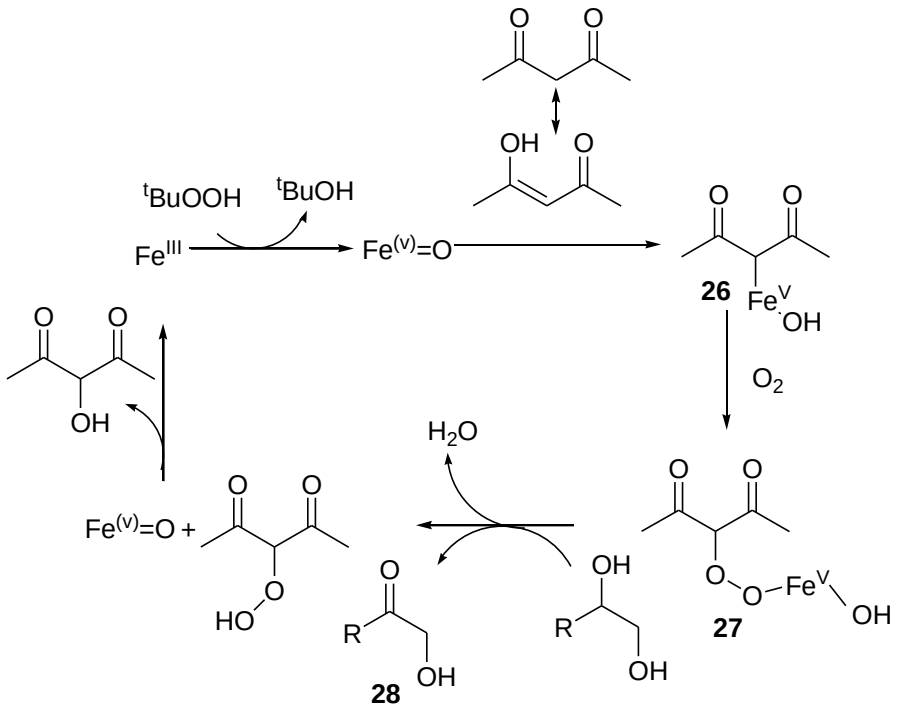
Plausible Mechanism

A plausible mechanism was proposed for the synthesis of substituted pyrazoles (Scheme 8). From screening experiments it has been found that when the reaction was carried out in absence of any ligand, only 13 % of the 1,3-diphenylpyrazoles was formed (Table 1, entry 8). But addition of the ligand acetyl acetone increases the product yield up to 70 % (Table 1, entry 6). This showed that acac has key role for the synthesis of substituted pyrazoles. Barton reported

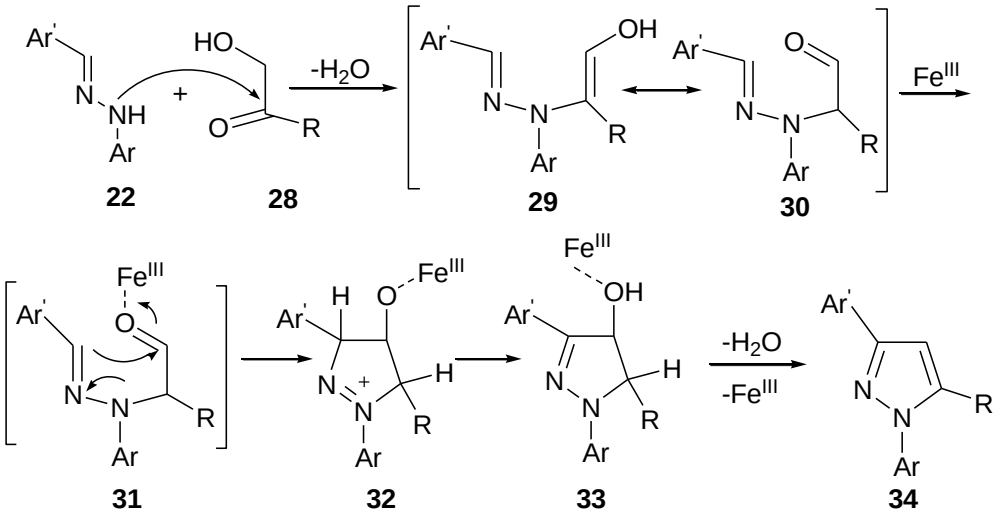
the oxidation of Fe(**III**) to Fe(**V**) in presence of TBHP.[27] Bolm described the Fe-mediated hydroxylation of 1,3-dicarbonyl compounds.[28]

Scheme 8

Step 1



Step 2



In line with the pioneering work of Barton[27] and Bolm,[28] we proposed that the Fe(**III**) in presence of TBHP oxidized to Fe(**V**). Subsequently, the Fe (**V**) species may undergo insertion to the active C-H bond of acetyl acetone to form an intermediate **26**, which in presence of O_2 form the inserted intermediate **27**. **27** may act as an oxidant to oxidize the vicinal diols to α-hydroxy carbonyl compounds **28**. In the subsequent step, the reaction of hydrazones **22** with the in situ formed α **28** lead to form the enols **29**, which undergo tautomerization to the keto derivatives **30**. Fe(**III**) then coordinates with the oxygen atom, there by activates the carbonyl carbon and facilitates the C-C bond formation by nucleophilic attack to form **32**.[25] The intermediate **32** undergoes rearrangement, followed by aromatization by the removal of water to the substituted pyrazoles **34**.

5.3. Conclusion

We have developed a mild protocol for the iron-catalyzed synthesis of substituted pyrazoles from simple vicinal diols and diaryl hydrazones. The synthesis of 1,3-disubstituted pyrazoles occurred at higher temperature and that of 1,3,5-trisubstituted pyrazoles at room temperature. This protocol was found to be tolerant to various electron-donating and -withdrawing substituents to the aromatic rings. This reaction was simple and afford a new route for the regioselective synthesis of 1,3- and 1,3,5-substituted pyrazoles.

5.4. Experimental

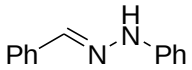
General procedure for the synthesis of hydrazine derivatives.[29]

A mixture containing aryl amines (5 mmol), conc. HCl (7 mL) and water (7 mL) was cooled to 0 $^{\circ}$C. To the above mixture sodium nitrite (7 mmol) was added and the resulting solution was stirred for 2 h at 0 $^{\circ}$C to get the diazotized compound. $SnCl_2$ (10 mmol) dissolved in conc. HCl (7 mL) was then added dropwise to the above mixture maintaining the temperature at 0 $^{\circ}$C and stirred for another 2 h. After completion of reaction, the resulting solid was filtered, dissolved in KOH (25 %) and extracted with ether. The extract was dried to get the hydrazine derivatives.

General procedure for the synthesis of hydrazone derivatives.

A mixture containing aldehydes (1 equiv) and arylhydrazines (1.1 equiv) in methanol was stirred at room temperature for appropriate time. The resulting solid was then filtered, washed with petroleum ether and dried to get the pure hydazones **22a-t**.

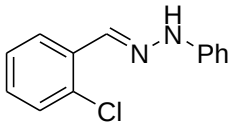
1-Benzylidene-2-phenylhydrazine (22a)



Following the general procedure, the reaction mixture containing benzaldehyde (500 mg, 4.71 mmol) and phenylhydrazine (560 mg, 5.18 mmol) was stirred at room temperature for 30 min. to afford 786 mg (85 %) of **22a** as a off white solid

MP: 152-154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.67 (m, 3H), 7.43-7.37 (m, 2H), 7.35-7.29 (m, 3H), 7.17-7.13 (m, 2H), 6.93-6.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (s), 137.3 (d), 135.3 (s), 129.3 (d), 128.6 (d), 128.4 (d), 126.2 (d), 120.1 (d), 112.7 (d).

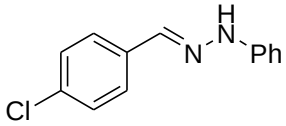
(E)-1-(2-Chlorobenzylidene)-2-phenylhydrazine (22b)



Following the general procedure, the reaction mixture containing 2-chlorobenzaldehyde (500 mg, 3.55 mmol) and phenylhydrazine (423 mg, 3.91 mmol) was stirred at room temperature for 3.5 h to afford 490 mg (60 %) of **22b** as a off white solid.

MP: 83-85 °C. IR (KBr): 3297, 3022, 1601, 1578, 1555, 1515, 1484, 1438, 1356, 1305 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.08 (m, 2H), 7.40-7.13 (m, 8H), 6.95-6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (s), 133.4 (d), 132.6 (s), 132.5 (s), 129.6 (d), 129.3 (d), 129.1 (d), 126.9 (d), 126.5 (d), 120.4 (d), 112.8 (d).

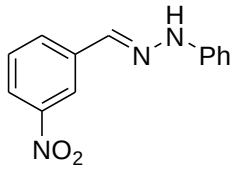
(E)-1-(4-Chlorobenzylidene)-2-phenylhydrazine (22c)



Following the general procedure, the reaction mixture containing 4-chlorobenzaldehyde (500 mg, 3.55 mmol) and phenylhydrazine (423 mg, 3.91 mmol) was stirred at room temperature for 30 min. to afford 530 mg (65 %) of **22c** as a off white solid.

MP: 125-127 °C. IR (KBr): 3308, 3051, 1598, 1557, 1516, 1485, 1443, 1399, 1355, 1307 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (bs, 1H), 7.62-7.57 (m, 3H), 7.37-7.27 (m, 4H), 7.14-7.11 (m, 2H), 6.94-6.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (s), 135.8 (d), 133.9 (s), 133.8 (s), 128.8 (d), 127.2 (d), 120.3 (d), 112.7 (d).

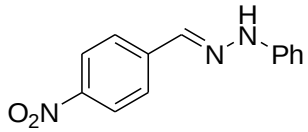
(E)-1-(3-Nitrobenzylidene)-2-phenylhydrazine (22d)



Following the general procedure, the reaction mixture containing 3-nitrobenzaldehyde (500 mg, 3.31 mmol) and phenylhydrazine (394 mg, 3.64 mmol) was stirred at room temperature for 2 h to afford 540 mg (68 %) of **22d** as a red solid.

MP: 120-122 °C. IR (KBr): 3297, 3026, 1600, 1571, 1534, 1491, 1443, 1357 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.15-8.11 (m, 1H), 8.01-7.97 (m, 1H), 7.72 (s, 1H), 7.57-7.51 (m, 1H), 7.36-7.30 (m, 2H), 7.19-7.15 (m, 2H), 6.98-6.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6 (s), 143.8 (s), 137.2 (s), 133.8 (d), 131.4 (d), 129.5 (d), 129.4 (d), 122.5 (d), 120.9 (d), 120.6 (d), 112.9 (d).

(E)-1-(4-Nitrobenzylidene)-2-phenylhydrazine (22e)

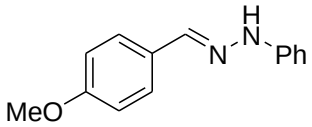


Following the general procedure, the reaction mixture containing 4-nitrobenzaldehyde (500 mg, 3.31 mmol) and phenylhydrazine (394 mg, 3.64 mmol) was stirred at room temperature for 30 min. to afford 640 mg (80 %) of **22e** as a red solid.

MP: 151-152 °C. IR (KBr): 3297, 3054, 2807, 1594, 1555, 1536, 1493, 1447, 1408, 1325 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.22 (m, 2H), 8.03 (bs, 1H), 7.81-7.76 (m, 2H), 7.71 (s,

1H), 7.37-7.31 (m, 2H), 7.19-7.15 (m, 2H), 7.00-6.94 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9 (s), 143.5 (s), 141.7 (s), 133.7 (d), 129.4 (d), 126.2 (d), 124.1 (d), 121.2 (d), 113.1 (d).

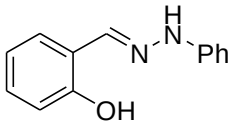
(E)-1-(4-Methoxybenzylidene)-2-phenylhydrazine (22f)



Following the general procedure, the reaction mixture containing 4-methoxybenzaldehyde (500 mg, 3.67 mmol) and phenylhydrazine (435 mg, 4.03 mmol) was stirred at room temperature for 1 h to afford 521 mg (63 %) of **22f** as a off white solid.

MP: 120-121 °C. IR (KBr): 3311, 2951, 2906, 2833, 1595, 1526, 1505, 1440, 1417, 1363 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.60 (m, 3H), 7.54 (bs, 1H), 7.32-7.26 (m, 2H), 7.14-7.10 (m, 2H), 6.95-6.87 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (s), 144.9 (s), 137.4 (d), 129.2 (d), 128.1 (s), 127.5 (d), 119.8 (d), 114.1 (d), 112.6 (d), 55.3 (q).

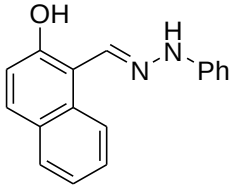
(E)-1-(2-Hydroxybenzylidene)-2-phenylhydrazine (22g)



Following the general procedure, the reaction mixture containing 2-hydroxybenzaldehyde (500 mg, 4.09 mmol) and phenylhydrazine (487 mg, 4.5 mmol) was stirred at room temperature for 3.5 hr to afford 503 mg (58 %) of **22g** as a off white solid.

MP: 120-121 °C. IR (KBr): 3314, 3032, 1599, 1554, 1522, 1491, 1445, 1413, 1356 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.54 (bs, 1H), 7.35-7.24 (m, 3H), 7.18-7.14 (m, 1H), 7.05-6.90 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (s), 143.3 (s), 141.1 (d), 130.0 (d), 129.5 (d),129.3 (d), 120.9 (d), 119.5 (d), 118.5 (s), 116.6 (d), 112.6 (d).

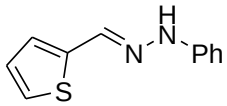
(E)-1-(2-Hydroxynapthylidene)-2-phenylhydrazine (22h)



Following the general procedure, the reaction mixture containing 2-hydroxynapthaldehyde (500 mg, 2.90 mmol) and phenylhydrazine (345 mg, 3.19 mmol) was stirred in ethanol at room temperature for 4.5 h to afford 456 mg (60%) of **22h** as a yellow solid.

MP: 156-159 °C. IR (KBr): 3319, 1619, 1588, 1532, 1488, 1467, 1331, 1301 $cm.^{-1}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 10.56 (s, 1H), 8.94 (s, 1H), 8.40-8.36 (m, 1H), 7.88-7.79 (m, 2H), 7.60-7.54 (m, 1H), 7.41-7.35 (m, 1H), 7.33-7.20 (m, 3H), 7.02-6.98 (m, 2H), 6.85-6.79 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.0 (s), 144.8 (s), 137.6 (s), 131.4 (s), 130.9 (d), 129.9 (d), 129.2 (d), 128.5 (s), 127.7 (d), 123.7 (d), 121.8 (d), 119.7 (d), 118.8 (d), 112.0 (d), 110.5 (d).

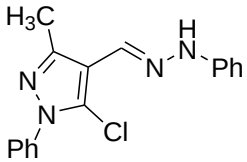
(E)-2-Phenyl-1-((thiophen-2-yl)methylene)hydrazine (22i)



Following the general procedure, the reaction mixture containing thiophen-2-aldehyde (500 mg, 4.46mmol) and phenylhydrazine (531 mg, 4.91 mmol) was stirred at room temperature for 3 h to afford 740 mg (82 %) of **22i** as a yellowish white solid.

MP: 132-134 °C. IR (KBr): 3321, 3096, 1646, 1601, 1535, 1504, 1447, 1356 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.55 (bs, 1H), 7.32-7.27 (m, 3H), 7.12-7.01 (m, 4H), 6.92-6.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (s), 140.4 (s), 132.1 (d), 129.3 (d), 127.2 (d), 126.4 (d), 125.9 (d), 120.2 (d), 112.7 (d).

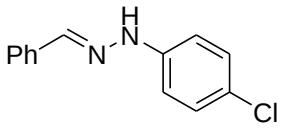
(E)-1-((5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)-2phenylhydrazine (22j)



Following the general procedure, the reaction mixture containing 5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-carbaldehyde (500 mg, 2.26 mmol) and phenylhydrazine (270 mg, 2.49 mmol) was stirred at room temperature for 4 h to afford 436 mg (62 %) of **22j** as a pale yellow solid.

MP: 137-139 °C. IR (KBr): 3242, 3048, 1599, 1544, 1493, 1441, 1409, 1379, 1365, 1314, 1294 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.63-7.56 (m, 3H), 7.53-7.48 (m, 2H), 7.45-7.40 (m, 1H), 7.34-7.29 (m, 2H), 7.10-7.06 (m, 2H), 6.92-6.86 (m, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (s), 144.7 (s), 137.9 (s), 129.3 (d), 129.3 (d), 129.0 (d), 128.1 (d), 125.5 (s), 124.8 (d), 119.9 (d), 114.2 (s), 112.4 (d), 15.05 (q).

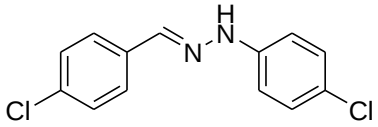
(E)-1-Benzylidene-2-(4-chlorophenyl)hydrazine (22k)



Following the general procedure, the reaction mixture containing benzaldehyde (500 mg, 4.7 mmol) and 4-chlorophenylhydrazine (664 mg, 5.17 mmol) was stirred at room temperature for 3 h to afford 815 mg (75 %) of **22k** as a off white solid.

MP: 107-109 °C. IR (KBr): 3314, 3055, 1593, 1560, 1513, 1484, 1443, 1408, 1286 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 3H), 7.43-7.22 (m, 5H), 7.08-7.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (s), 137.9 (d), 135.0 (s), 129.2 (d), 128.6 (d), 126.2 (d), 124.6 (s), 113.8 (d).

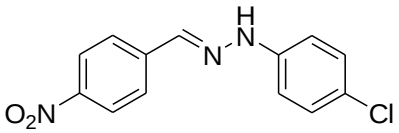
(E)-1-(4-Chlorobenzylidene)-2-(4-chlorophenyl)hydrazine (22l)



Following the general procedure, the reaction mixture containing 4-chlorobenzaldehyde (500 mg, 3.55 mmol) and 4-chlorophenylhydrazine (503 mg, 3.91 mmol) was stirred at room temperature for 5 h to afford 744 mg (80 %) of **22l** as a yellowish white solid.

MP: 142-144 °C. IR (KBr): 3304, 1596, 1557, 1508, 1483, 1400, 1348, 1304, 1287 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.65 (s, 1H), 7.61-7.56 (m, 2H), 7.38-7.33 (m, 2H), 7.27-7.21 (m, 2H), 7.08-7.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0 (s), 136.4 (d), 134.2 (s), 133.5 (s), 129.2 (d), 128.8 (d), 127.3 (d), 124.8 (s), 113.8 (d).

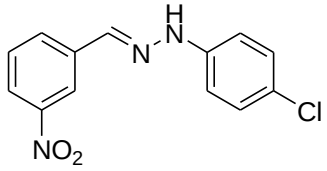
(E)-1-(4-Nitrobenzylidene)-2-(4-chlorophenyl)hydrazine (22m)



Following the general procedure, the reaction mixture containing 4-nitrobenzaldehyde (500 mg, 3.31 mmol) and 4-chlorophenylhydrazine (468 mg, 3.64 mmol) was stirred at room temperature for 4 h to afford 593 mg (65 %) of **22m** as a red solid.

MP: 124-126 °C. IR (KBr): 3286, 3042, 1592, 1553, 1527, 1496, 1484, 1408, 1331 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.22 (m, 2H), 8.01 (bs, 1H), 7.81-7.76 (m, 2H), 7.72 (s, 1H), 7.30-7.25 (m, 2H), 7.13-7.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 (s), 142.2 (s), 141.3 (s), 134.4 (d), 129.3 (d), 126.3 (d), 125.9 (s), 124.1 (d), 114.2 (d).

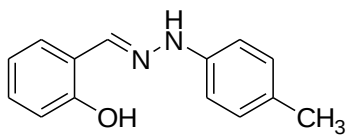
(E)-1-(3-Nitrobenzylidene)-2-(4-chlorophenyl)hydrazine (22n)



Following the general procedure, the reaction mixture containing 3-nitrobenzaldehyde (500 mg, 3.31 mmol) and 4-chlorophenylhydrazine (468 mg, 3.64 mmol) was stirred at room temperature for 1 h to afford 548 mg (60 %) of **22n** as a yellow solid.

MP: 137-138 °C. IR (KBr): 3321, 3027, 1604, 1585, 1565, 1521, 1483, 1426, 1408, 1341, 1302, 1285 $cm.^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47-8.44 (m, 1H), 8.17-8.12 (m, 1H), 8.00-7.96 (m, 1H), 7.90 (bs, 1H), 7.73 (s, 1H), 7.58-7.52 (m, 1H), 7.30-7.24 (m, 2H), 7.12-7.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (s), 142.4 (s), 136.9 (s), 134.5 (d), 131.4 (d), 129.5 (d), 129.3 (d), 125.5 (s), 122.8 (d), 120.7 (d), 114.1 (d).

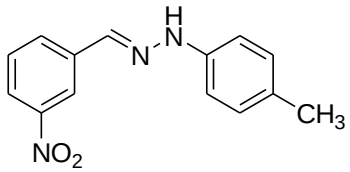
(E)-1-(2-Hydroxybenzylidene)-2-p-tolylhydrazine (22p)



Following the general procedure, the reaction mixture containing 2-hydroxybenzaldehyde (500 mg, 4.1 mmol) and 4-tolylhydrazine (550 mg, 4.5 mmol) was stirred at room temperature for 1 h to afford 509 mg (55 %) of **22p** as a yellowish white solid.

MP: 123-125 °C. IR (KBr): 3308, 3049, 3005, 2855, 1618, 1564, 1522, 1504, 1487, 1412, 1352, 1292 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.95 (s, 1H), 7.85 (s, 1H), 7.46 (bs, 1H), 7.27-7.22 (m, 1H), 7.18-7.10 (m, 3H), 7.03-6.99 (m, 1H), 6.94-6.88 (m, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (s), 141.1 (s), 140.6 (d), 130.3 (s), 130.0 (d), 129.8 (d), 129.2 (d), 119.4 (d), 118.6 (d), 116.5 (d), 112.7 (d), 20.6 (q).

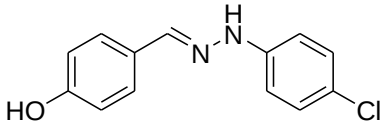
(E)-1-(3-Nitrobenzylidene)-2-p-tolylhydrazine (22q)



Following the general procedure, the reaction mixture containing 3-nitrobenzaldehyde (500 mg, 3.31 mmol) and 4-tolylhydrazine (444 mg, 3.64 mmol) was stirred at room temperature for 2 h to afford 603 mg (75 %) of **22q** as a yellow solid.

MP: 143-145 °C. IR (KBr): 3305, 2859, 1610, 1580, 1517, 1348, 1314, 1284 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46-8.43 (m, 1H), 8.13-8.09 (m, 1H), 8.00-7.96 (m, 1H), 7.69 (bs, 1H), 7.56-7.50 (m, 1H), 7.15-7.04 (m, 4H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6 (s), 141.5 (s), 137.4 (s), 133.3 (d), 131.3 (d), 130.2 (s), 129.9 (d), 122.3 (d), 120.5 (d), 112.9 (d), 20.6 (q).

(E)-1-(4-Hydroxybenzylidene)-2-(4-chlorophenyl)hydrazine (22s)



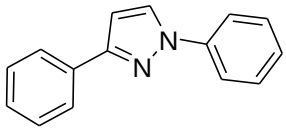
Following the general procedure, the reaction mixture containing 4-hydroxybenzaldehyde (500 mg, 4.09 mmol) and 4-chlorophenylhydrazine (578 mg, 4.5 mmol) was stirred at room temperature for 3 h to afford 745 mg (75 %) of **22s** as a off white solid.

MP: 128-130 °C. IR (KBr): 3417, 3030, 2969, 1736, 1647, 1599, 1505, 1479, 1440, 1406, 1366 cm.$^{-1}$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (bs, 1H), 7.79-7.74 (s, 1H), 7.49-7.45 (m, 2H), 7.21-7.03 (m, 2H), 6.95-6.91 (m, 2H), 6.81-6.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.3 (s), 145.0 (s), 138.4 (d), 129.2 (d), 127.7 (d), 127.0 (s), 121.7 (s), 116.0 (d), 113.5 (d).

General procedure for the synthesis of 1,3-disubstituted pyrazoles.

A mixture of diarylhydrazones (100 mg), $FeCl_3$ (5 mol %), and ethylene glycol (2 mL) was stirred under O_2 atmosphere at rt. To the resulting mixture acetyl acetone (2 equiv) followed by TBHP (1 equiv) was added dropwise, and the temperature was slowly increased to 80-120 °C. After being stirred at the appropriate temperature for 6 h (completion of the reaction was monitored by TLC), the reaction mixture was cooled to room temperature. Dichloromethane was added. The organic layer was washed with water, dried over Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate and petroleum ether as eluent to afford **24a-q**.

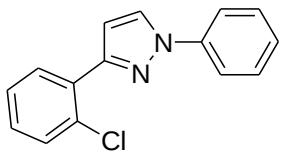
1,3-Diphenyl-1H-pyrazole (24a)[30]



Following the general procedure, the reaction was stirred at 120 °C to give 83 mg (75 %) of **24a** as a colourless solid.

MP: 80-82 °C. IR (KBr): 1597, 1527, 1504, 1456, 1361 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 3H), 7.80-7.76 (m, 2H), 7.51-7.40 (m, 4H), 7.38-7.26 (m, 2H), 6.79 (d, 1H, J = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (s), 140.2 (s), 133.1 (s), 129.4 (d), 128.6 (d), 128.0 (d), 128.0 (d), 126.3 (d), 125.8 (d), 119.0 (d), 105.0 (d). Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72; Found: C, 80.46; H, 5.36; N, 11.50. MS (ESI): *m/z* (relative intensity) 243 ($[M+Na]^+$, 100 %), 221 ($[M+H]$,$^+$ 37 %).

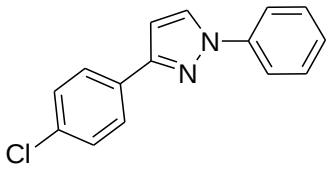
3-(2-Chlorophenyl)-1-phenyl-1H-pyrazole (24b)[31]



Following the general procedure, the reaction was stirred at 120 °C to give 68 mg (62 %) of **24b** as a colourless solid.

MP: 134-136 °C. IR (KBr): 3050, 1597, 1503, 1448, 1386, 1348 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 2.4 Hz), 7.99-7.95 (m, 1H), 7.80 (d, 2H, *J* = 8 Hz), 7.49 (t, 3H, *J* = 7.6 Hz), 7.39-7.29 (m, 3H), 7.03 (d, 1H, *J* = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (s), 140.1 (s), 132.4 (s), 132.1 (s), 130.7 (d), 130.3 (d), 129.4 (d), 129.0 (d), 127.1 (d), 126.8 (d), 126.5 (d), 119.1 (d), 109.0 (d). Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00; Cl, 13.92 Found: C, 70.03; H, 5.12; N, 10.45. MS (ESI): *m/z* (relative intensity) 277 ([M+Na],$^{+}$ 100 %), 255 ([M+H],$^{+}$ 45 %).

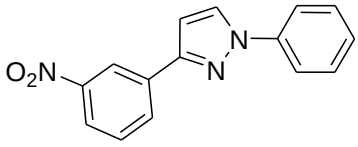
3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole (24c) [30]



Following the general procedure, the reaction was stirred at 120 °C to give 75 mg (68 %) of **24c** as a colourless solid.

MP: 118 °C. IR (KBr): 3052, 2924, 1596, 1507, 1442, 1410, 1262 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H, *J* = 2.8 Hz), 7.87 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 7.6 Hz), 7.52-7.46 (m, 2H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.35-7.30 (m, 1H), 6.77 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (s), 140.1 (s), 133.7 (s), 131.6 (s), 129.4 (d), 128.8 (d), 128.1 (d), 127.0 (d), 126.5 (d), 119.0 (d), 104.9 (d). Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00; Cl, 13.92 Found: C, 70.25; H, 4.89; N, 11.40. MS (ESI): *m/z* (relative intensity) 277 ([M+Na],$^{+}$ 100 %), 255 ([M+H],$^{+}$ 39 %).

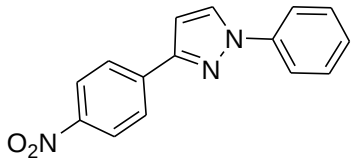
3-(3-Nitrophenyl)-1-phenyl-1H-pyrazole (24d)



Following the general procedure, the reaction was stirred at 100 °C to give 68 mg (62 %) of **24d** as a yellow solid.

MP: 110-112 °C. IR (KBr): 1596, 1518, 1455, 1345 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, *J* = 0.8 Hz), 8.22-8.18 (m, 2H), 8.03 (d, 1H, *J* = 2.8 Hz), 7.80 (d, 2H, *J* = 7.6 Hz), 7.64-7.48 (m, 3H), 7.38-7.32 (m, 1H), 6.88 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (s), 148.7 (s), 139.9 (s), 135.0 (s), 131.4 (d), 129.5 (d), 128.5 (d), 126.8 (d), 122.4 (d), 120.6 (d), 119.1 (d), 105.2 (d). Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; O, 12.06 Found: C, 67.36; H, 4.10; N, 14.73. MS (ESI): *m/z* (relative intensity) 288 ([M+Na],$^{+}$ 100 %), 266 ([M+H],$^{+}$ 23 %).

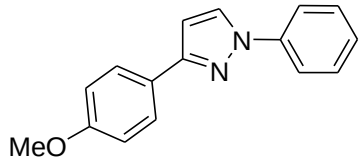
***3-(4-Nitrophenyl)-1-phenyl-1H-pyrazole (24e)*[31]**



Following the general procedure, the reaction was stirred at 120 °C to give 80 mg (73 %) of **24e** as a yellow solid.

MP: 138-140 °C. IR (KBr): 1597, 1557, 1506, 1457, 1418, 1334 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 2H, *J* = 8.8 Hz), 8.09 (d, 2H, *J* = 8.8 Hz), 8.03 (d, 1H, *J* = 2.4 Hz), 7.80 (d, 2H, *J* = 7.6 Hz), 7.55-7.49 (m, 2H), 7.39-7.34 (m, 1H), 6.89 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (s), 147.3 (s), 139.9 (s), 139.4 (s), 129.5 (d), 128.6 (d), 127.0 (d), 126.2 (d), 124.0 (d), 119.2 (d), 105.8 (d). Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; O, 12.06 Found: C, 67.69; H, 4.12; N, 15.60. MS (ESI): *m/z* (relative intensity) 288 ([M+Na],$^{+}$ 100 %), 266 ([M+H],$^{+}$ 24 %).

***3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazole (24f)*[30]**

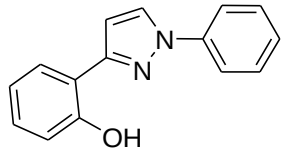


Following the general procedure, the reaction was stirred at 120 °C to give 77 mg (70 %) of **24f** as a colourless solid.

MP: 102-104 °C. IR (KBr): 3141, 3059, 2959, 1596, 1510, 1452, 1389, 1358 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H, *J* = 2.4 Hz), 7.89-7.85 (m, 2H), 7.80-7.76 (m, 2H), 7.51-7.45

(m, 2H), 7.32-7.30 (m, 1H), 7.01-6.97 (m, 2H), 6.72 (d, 1H, *J* = 2.4 Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (s), 152.7 (s), 140.3 (s), 129.3 (d), 127.8 (d), 127.1 (d), 126.1 (d), 125.9 (s), 118.9 (d), 114.0 (d), 104.5 (d), 55.3 (q). Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19; O, 6.39 Found: C, 76.38; H, 5.66; N, 10.98. MS (ESI): *m/z* (relative intensity) 273 ([M+Na],$^+$ 100 %), 251 ([M+H],$^+$ 70 %).

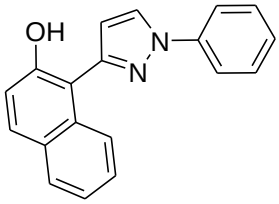
2-(1-Phenyl-1H-pyrazol-3-yl)phenol (24g)[31]



Following the general procedure, the reaction was stirred at 120 °C to give 70 mg (63 %) of **24g** as a colourless solid.

MP: 102 °C. IR (KBr): 3142, 3050, 2951, 2920, 2854, 1621, 1599, 1523, 1506, 1451, 1403, 1362, cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s), 7.99 (d, 1H, *J* = 2.8 Hz), 7.70 (d, 1H, *J* = 8 Hz), 7.64 (d, 1H, *J* = 8 Hz), 7.54-7.48 (m, 2H), 7.38-7.26 (m, 2H), 7.10 (d, 1H, *J* = 8 Hz), 6.99-6.94 (m, 1H), 6.88 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (s), 152.9 (s), 139.2 (s), 129.6 (d), 129.6 (d), 127.7 (d), 126.8 (d), 126.5 (d), 119.3 (d), 118.8 (d), 117.2 (d), 116.2 (s), 104.5 (d). Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; O, 6.77 Found: C, 76.40; H, 4.78; N, 11.36. MS (ESI): *m/z* (relative intensity) 259 ([M+Na],$^+$ 100 %), 237 ([M+H],$^+$ 55 %).

1-(1-Phenyl-1H-pyrazol-3-yl)naphthol (24h)

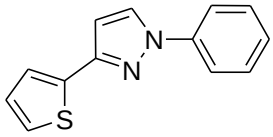


Following the general procedure, the reaction was stirred at 120 °C to give 71 mg (65 %) of **24h** as a colourless solid.

MP: 74-76 °C. IR (KBr): 3145, 3048, 2912, 1598, 1547, 1528, 1509, 1464, 1391, 1368, 1336 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.33 (d, 1H, *J* = 8.8 Hz), 8.15 (d, 1H, *J* = 2.4

Hz), 7.86-7.77 (m, 4H), 7.56-7.48 (m, 3H), 7.41-7.31 (m, 3H), 7.04 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7 (s), 150.4 (s), 139.4 (s), 132.0 (s), 130.4 (d), 129.6 (d), 129.0 (s), 128.7 (d), 127.9 (d), 126.8 (d), 126.7 (d), 123.8 (d), 123.0 (d), 118.9 (d), 118.8 (d), 109.8 (s), 109.5 (d). Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78; O, 5.59 Found: C, 79.11; H, 4.93; N, 9.72. MS (ESI): *m/z* (relative intensity) 309 ([M+Na],$^+$ 100 %), 287 ([M+H],$^+$ 30 %).

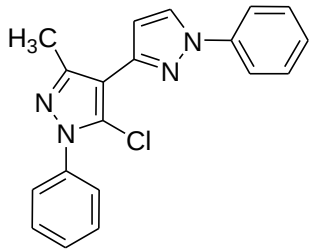
1-Phenyl(3-thiophen-2-yl)-1H-pyrazole (24i)[32]



Following the general procedure, the reaction was stirred at 120 °C to give 75 mg (68 %) of **24i** as a colourless solid.

MP: 65 °C. IR (KBr): 3066, 2920, 1597, 1559, 1506, 1460, 1375 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.76 (d, 2H, *J* = 8 Hz), 7.51-7.44 (m, 3H), 7.34-7.29 (m, 2H), 7.13-7.10 (m, 1H), 6.70 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 (s), 139.9 (s), 136.3 (s), 129.4 (d), 128.0 (d), 127.4 (d), 126.4 (d), 124.9 (d), 124.2 (d), 119.0 (d), 105.0 (d). Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38; S, 14.17 Found: C, 68.78; H, 4.40; N, 12.46; S, 13.28. MS (ESI): *m/z* (relative intensity) 249 ([M+Na],$^+$ 100 %), 227 ([M+H],$^+$ 56 %).

3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazole (24j)

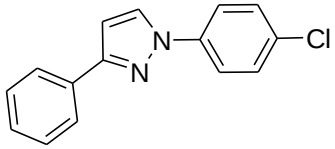


Following the general procedure, the reaction was stirred at 100 °C to give 70 mg (65 %) of **24j** as a colourless solid.

MP: 110-112 °C. IR (KBr): 3048, 2922, 1595, 1506, 1450, 1408, 1378, 1337 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 1H, *J* = 2.4 Hz), 7.82-7.78 (m, 2H), 7.63-7.59 (m, 2H), 7.55-7.42 (m, 5H), 7.34-7.29 (m, 1H), 6.87 (d, 1H, *J* = 2.8 Hz), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (s), 144.9 (s), 140.1 (s), 138.2 (s), 129.4 (d), 129.2 (s), 129.0 (d), 128.1 (d), 126.9 (d),

126.2 (d), 125.2 (d), 118.7 (d), 112.2 (s), 106.6 (d), 14.6 (q). Anal. Calcd. for $C_{19}H_{15}N_4Cl$: C, 68.16; H, 4.52; N, 16.73; Cl, 10.59 Found: C, 67.71; H, 4.48; N, 16.59. MS (ESI) *m/z* (relative intensity) 357 ($[M+Na]^+$ 100 %), 335 ($[M+H]^+$ 68 %).

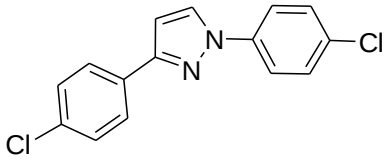
***1-(4-Chlorophenyl)-3-phenyl-1H-pyrazole (24k)*[33]**



Following the general procedure, the reaction was stirred at 100 °C to give 85 mg (77 %) of **24k** as a colourless solid.

MP: 132-133 °C. IR (KBr): 3059, 1594, 1530, 1505, 1491, 1451, 1385 $cm.^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (m, 3H), 7.76-7.72 (m, 2H,), 7.48-7.44 (m, 4H), 7.40-7.34 (m, 1H), 6.80 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (s), 138.7 (s), 132.8 (s), 131.7 (s), 129.4 (d), 128.7 (d), 128.2 (d), 127.9 (d), 125.8 (d), 120.0 (d), 105.4 (d). Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00; Cl, 13.92 Found: C, 70.30; H, 4.48; N, 10.92. MS (ESI) *m/z* (relative intensity) 277 ($[M+Na]^+$ 54 %), 255 ($[M+H]^+$ 30 %).

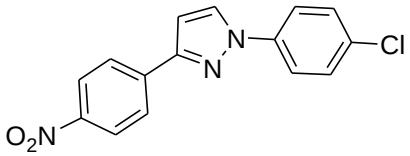
1,3-bis(4-Chlorophenyl)-1H-pyrazole (24l)



Following the general procedure, the reaction was stirred at 100 °C to give 92 mg (85 %) of **24l** as a colourless solid.

MP: 136 °C. IR (KBr): 3145, 3048, 1594, 1565, 1501, 1443, 1419, 1381 $cm.^{-1}$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H, *J* = 2.4 Hz), 7.88-7.82 (m, 2H), 7.75-7.69 (m, 2H), 7.48-7.40 (m, 4H), 6.76 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0 (s), 138.6 (s), 133.9 (s), 131.9 (s), 131.4 (s), 129.5 (d), 128.8 (d), 128.0 (d), 127.0 (d), 120.1 (d), 105.3 (d). Anal. Calcd. for $C_{15}H_{10}N_2Cl_2$: C, 62.30; H, 3.49; N, 9.69 Found: C, 61.94; H, 3.41; N, 9.59. MS (ESI) *m/z* relative intensity 289 ($[M+H]^+$ 40%).

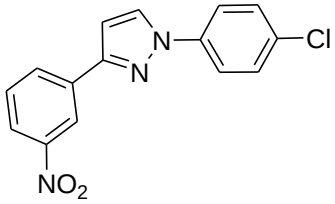
1-(4-Chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazole (24m)[34]



Following the general procedure, the reaction was stirred at 80 °C to give 77 mg (71 %) of the 1,3-diarylpyrazole **24m** as a yellow solid.

MP: 168-170 °C. IR (KBr): 2920, 1598, 1555, 1511, 1449, 1422, 1343 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33-8.29 (d, 2H, *J* = 8.8 Hz), 8.10-8.06 (d, 2H, *J* = 8.8 Hz), 8.00 (d, 1H, *J* = 2.4 Hz), 7.77-7.73 (d, 2H, *J* = 8.4 Hz), 7.51-7.46 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (s), 147.4 (s), 139.1 (s), 138.4 (s), 132.5 (s), 129.6 (d), 128.5 (d), 126.2 (d), 124.1 (d), 120.3 (d), 106.2 (d). Anal. Calcd. for $C_{15}H_{10}N_3O_2Cl$: C, 60.11; H, 3.36; N, 14.02; Cl, 11.83; O, 10.68 Found: C, 59.36; H, 3.10; N, 14.06.

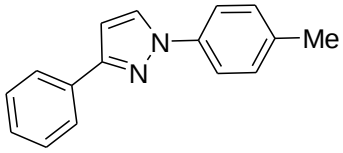
1-(4-Chlorophenyl)-3-(3-nitrophenyl)-1H-pyrazole (24n)



Following the general procedure, the reaction was stirred at 90 °C to give 80 mg (74%) of **24n** as a yellow solid.

MP: 144-146 °C. IR (KBr): 3083, 1594, 1519, 1501, 1433, 1416, 1346, 1308 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.28-8.18 (m, 2H), 8.00 (d, 1H, *J* = 2.8 Hz), 7.77-7.72 (m, 2H), 7.62 (t, 1H, *J* = 8 Hz), 7.51-7.45 (m, 2H), 6.89 (d, 1H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (s), 148.7 (s), 138.4 (s), 134.7 (s), 132.3 (s), 131.5 (d), 129.6 (d), 128.4 (d), 122.6 (d), 120.6 (d), 120.2 (d), 105.6 (d). Anal. Calcd. for $C_{15}H_{10}N_3O_2Cl$: C, 60.11; H, 3.36; N, 14.02; Cl, 11.83; O, 10.68 Found: C, 60.51; H, 3.59; N, 13.91. MS (ESI): *m/z* (relative intensity) 300 ([M+H],$^{+}$ 48 %).

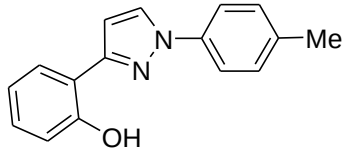
3-Phenyl-1-p-tolyl-1H-pyrazole (24o)[30]



Following the general procedure, the reaction was stirred at 90 °C to give 67 mg (61 %) of **24o** as a colourless solid.

MP: 110-111 °C. IR (KBr): 3145, 3029, 1605, 1521, 1453, 1389, 1364 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.91 (m, 3H), 7.69-7.64 (m, 2H,), 7.48-7.42 (m, 2H), 7.38-7.32 (m, 1H), 7.30-7.26 (m, 2H), 6.78 (d, 1H, *J* = 2.8 Hz), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (s), 138.0 (s), 136.1 (s), 133.2 (s), 129.9 (d), 128.6 (d), 127.9 (d), 125.8 (d), 119.0 (d), 104.7 (d), 20.9 (q) Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96 Found: C, 81.81; H, 6.05; N, 12.02. MS (ESI): *m/z* (relative intensity) 257 ([M+Na],$^{+}$ 69 %), 235 ([M+H],$^{+}$ 100 %).

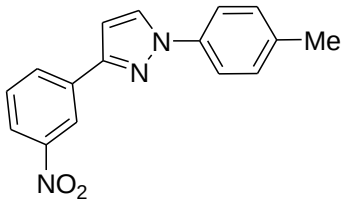
2-(1-p-Tolyl-1H-pyrazol-3-yl)phenol (24p)



Following the general procedure, the reaction was stirred at 90 °C to give 64 mg (58 %) of **24p** as a colourless solid.

MP: 117-119 °C. IR (KBr): 3152, 3044, 2955, 1619, 1584, 1519, 1454, 1402, 1365, 1299 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.95 (d, 1H, *J* = 2.8 Hz), 7.66-7.56 (m, 3H), 7.32-7.24 (m, 4H), 7.08 (d, 1H, *J* = 8 Hz), 7.07-6.93 (m, 1H), 6.86 (d, 1H, *J* = 3.2 Hz), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (s), 152.6 (s), 137.1 (s), 136.7 (s), 130.1 (d), 129.5 (d), 127.6 (d), 126.5 (d), 119.3 (d), 118.8 (d), 117.1 (d), 116.3 (s), 104.2 (d), 20.9 (q). Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19; O, 6.39 Found: C, 76.48; H, 4.32; N, 12.20.

3-(3-Nitrophenyl)-1-p-tolyl-1H-pyrazole (24q)



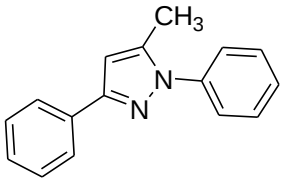
Following the general procedure, the reaction was stirred at 80 °C to give 65 mg (60 %) of **24q** as a yellow solid

MP: 113-115 °C. IR (KBr): 3032, 2921, 2854, 1609, 1580, 1522, 1455, 1347 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76-8.74 (m, 1H), 8.26 (d, 1H, *J* = 8 Hz), 8.20-8.16 (m, 1H), 7.97 (d, 1H, *J* = 2.4 Hz),7.67 (d, 2H, *J* = 8.4 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 1H, *J* = 2.4 Hz), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (s), 148.7 (s), 137.7 (s), 136.7 (s), 135.0 (s), 131.4 (d), 130.0 (d), 129.5 (d), 128.4 (d), 122.4 (d), 120.5 (d), 119.1 (d), 105.0 (d), 20.9 (q). Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05; O, 11.46 Found: C, 67.98; H, 5.07; N, 15.64. MS (ESI) *m/z* (relative intensity) 302 ([M+Na],$^{+}$ 100 %), 280 ([M+H],$^{+}$ 43 %).

General procedure for the synthesis of 1,3,5-substituted pyrazoles

A mixture of diaryl hydrazones **22** (100 mg) and $FeCl_3$ (5 mol %) in 1,2-propanediol (2 mL) was stirred under O_2 atmosphere. To the resulting mixture acetyl acetone (2 equiv) followed by TBHP (1 equiv) was added dropwise at room temperature. After stirring for 1 hr at rt (completion of the reaction was monitored by TLC) dichloromethane was added. The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and petroleum ether as the eluent to afford 1,3,5-substituted pyrazoles **25a-g**.

5-Methyl-1,3-diphenyl-1H-pyrazole (25a)[35]

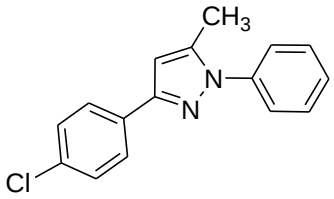


Following the general procedure, the reaction was stirred at rt to give 66 mg (55 %) of the 1,3-diaryl-4-methylpyrazole **25a** as a yellow liquid.

IR (neat): 3060, 2924, 1597, 1549, 1500, 1456, 1412, 1365 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.86 (m, 2H), 7.57-7.48 (m, 4H), 7.45-7.39 (m, 3H), 7.36-7.32 (m, 1H), 6.55 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5 (s), 140.1 (s), 139.9 (s), 133.3 (s), 129.0 (d), 128.5

(d), 127.7 (d), 127.6 (d), 125.7 (d), 125.0 (d), 104.3 (d), 12.5 (q). MS (ESI): *m/z* (relative intensity) 257 ([M+Na],$^{+}$ 100 %), 235 ([M+H],$^{+}$ 88 %).

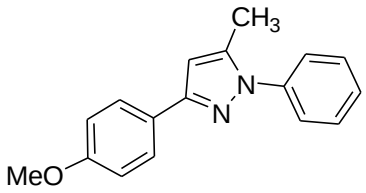
3-(4-Chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole (25b)



Following the general procedure, the reaction was stirred at rt to give 60 mg (52 %) of **25b** as a colourless solid.

MP: 80 °C. IR (KBr): 3059, 2920, 1597, 1547, 1501, 1453, 1431, 1397, 1360 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (t, 2H, *J* = 2 Hz), 7.55- 7.48 (m, 4H), 7.45-7.36 (m, 3H), 6.51 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4 (s), 140.4 (s), 139.8 (s), 133.4 (s), 131.9 (s), 129.1 (d), 128.7 (d), 127.7 (d), 126.9 (d), 124.9 (d), 104.3 (d), 12.5 (q) MS (ESI): *m/z* (relative intensity) 291 ([M+Na],$^{+}$ 97 %), 269 ([M+H],$^{+}$ 100 %).

3-(4-Methoxyphenyl)-5-methyl-1-phenyl-1H-pyrazole (25c)

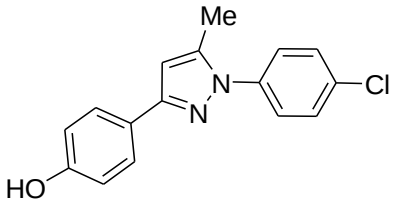


Following the general procedure, the reaction was stirred at rt to give 68 mg (58 %) of **25c** as a colourless solid.

MP: 102-104 °C. IR (KBr): 3059, 2956, 1597, 1523, 1500, 1453, 1432, 1404, 1362, 1292 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 2H), 7.56-7.47 (m, 4H), 7.42-7.37 (m, 1H), 6.98-6.93 (m, 2H), 6.47 (s, 1H), 3.85 (s, 3H), 2.39 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (s), 151.3 (s), 140.0 (s), 139.9 (s), 129.0 (d), 127.4 (d), 126.9 (d), 126.1 (s), 124.9 (d), 113.9 (d), 103.9 (d), 55.2 (q), 12.5 (q). Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; O, 6.05

Found: C, 77.05; H, 6.02; N, 11.32. MS (ESI) *m/z* (relative intensity) 287 ([M+Na],$^{+}$ 100 %), 265 ([M+H],$^{+}$ 85 %).

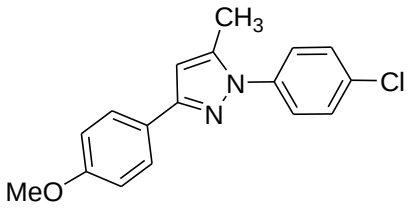
4-(1-(4-Chlorophenyl)-5-methyl-1H-pyrazol-3-yl)phenol (25d)



Following the general procedure, the reaction was stirred at rt to give 61 mg (52 %) of **25d** as a colourless solid.

MP: 176-178 °C. IR (KBr): 2984, 1611, 1551, 1524, 1496, 1466, 1435, 1404, 1362 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.67 (m, 2H), 7.46 (m, 4H), 6.85-6.81 (m, 2H), 6.46 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (s), 151.7 (s), 140.2 (s), 138.3 (s), 133.2 (s), 129.2 (d), 127.2 (d), 126.0 (d), 125.6 (s), 115.5 (d), 104.3 (d), 12.5 (q). Anal. Calcd. for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60; N, 9.84; O, 5.62; Cl, 12.45 Found: C, 66.80; H, 4.30; N, 10.03. MS (ESI): *m/z* (relative intensity) 307 ([M+Na],$^{+}$ 51 %), 285 ([M+H],$^{+}$ 46 %).

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-methyl-1H-pyrazole (25e)

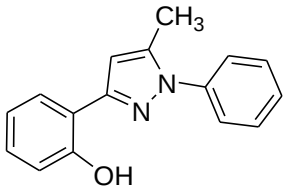


Following the general procedure, the reaction was stirred at rt to give 64 mg (56 %) of **25e** as a colourless solid.

MP: 97 °C. IR (KBr): 3063, 2998, 2959, 2932, 2833, 1612, 1523, 1497, 1462, 1434, 1401, 1363 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.76 (m, 2H), 7.49-7.46 (m, 4H), 6.98-6.93 (m, 2H), 6.47 (s, 1H), 3.86 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5 (s), 151.6 (s), 140.0 (s), 138.5 (s), 133.1 (s), 129.2 (d), 126.9 (d), 125.9 (s), 114.0 (d), 104.3 (d), 55.2 (q), 12.5 (q). Anal. Calcd. for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38; O, 5.36, Cl, 11.87 Found: C,

68.44; H, 4.83; N, 10.13. MS (ESI) *m/z* (relative intensity) 321 ([M+Na],$^{+}$ 91 %), 299 ([M+H],$^{+}$ 100 %).

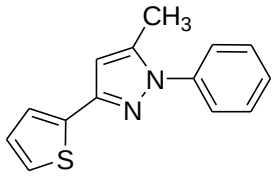
2-(5-Methyl-1-phenyl-1H-pyrazol-3-yl)phenol (25f)



Following the general procedure, the reaction was stirred at rt to give 60 mg (51 %) of **25f** as a colourless liquid.

IR (neat): 3133, 3102, 3056, 1619, 1596, 1548, 1501, 1458, 1367, 1295 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (s, 1H), 7.60 (d, 1H, *J* = 1.6 Hz), 7.59-7.49 (m, 4H), 7.47-7.41 (m, 1H), 7.27-7.21 (m, 1H), 7.06-7.02 (m, 1H), 6.97-6.91 (m, 1H), 6.61 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (s), 151.6 (s), 139.9 (s), 139.1 (s), 129.2 (d), 129.1 (d), 127.9 (d), 126.3 (d), 124.6 (d), 119.1 (d), 117.0 (d), 116.4 (s), 103.8 (d), 12.4 (q).

5-Methyl-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (25g)



Following the general procedure, the reaction was stirred at rt to give 71 mg (60 %) of **25g** as a colourless oil.

IR (neat): 3067, 2962, 1596, 1565, 1532, 1500, 1424, 1375, 1327 cm.$^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.46 (m, 4H), 7.43-7.37 (m, 2H), 7.28-7.26 (m, 1H), 7.10-7.06 (m, 1H), 6.45 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8 (s), 140.2 (s), 139.6 (s), 136.6 (s), 129.1 (d), 127.7 (d), 127.4 (d), 125.0 (d), 124.5 (d), 123.8 (d), 104.3 (d), 12.5 (q). MS (ESI) *m/z* (relative intensity) 263 ([M+Na],$^{+}$ 100 %), 241 ([M+H],$^{+}$ 55 %).

5.5. References

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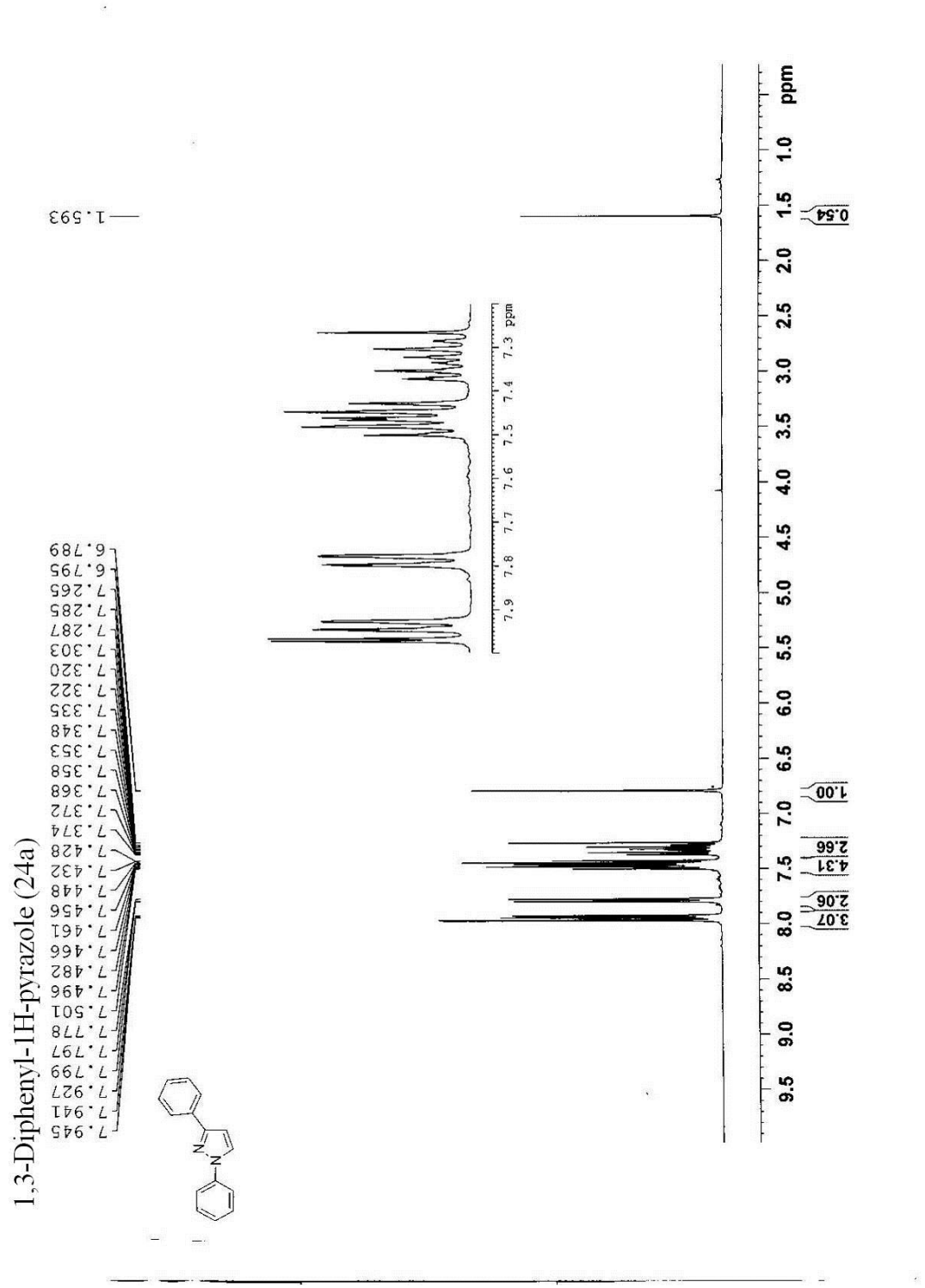
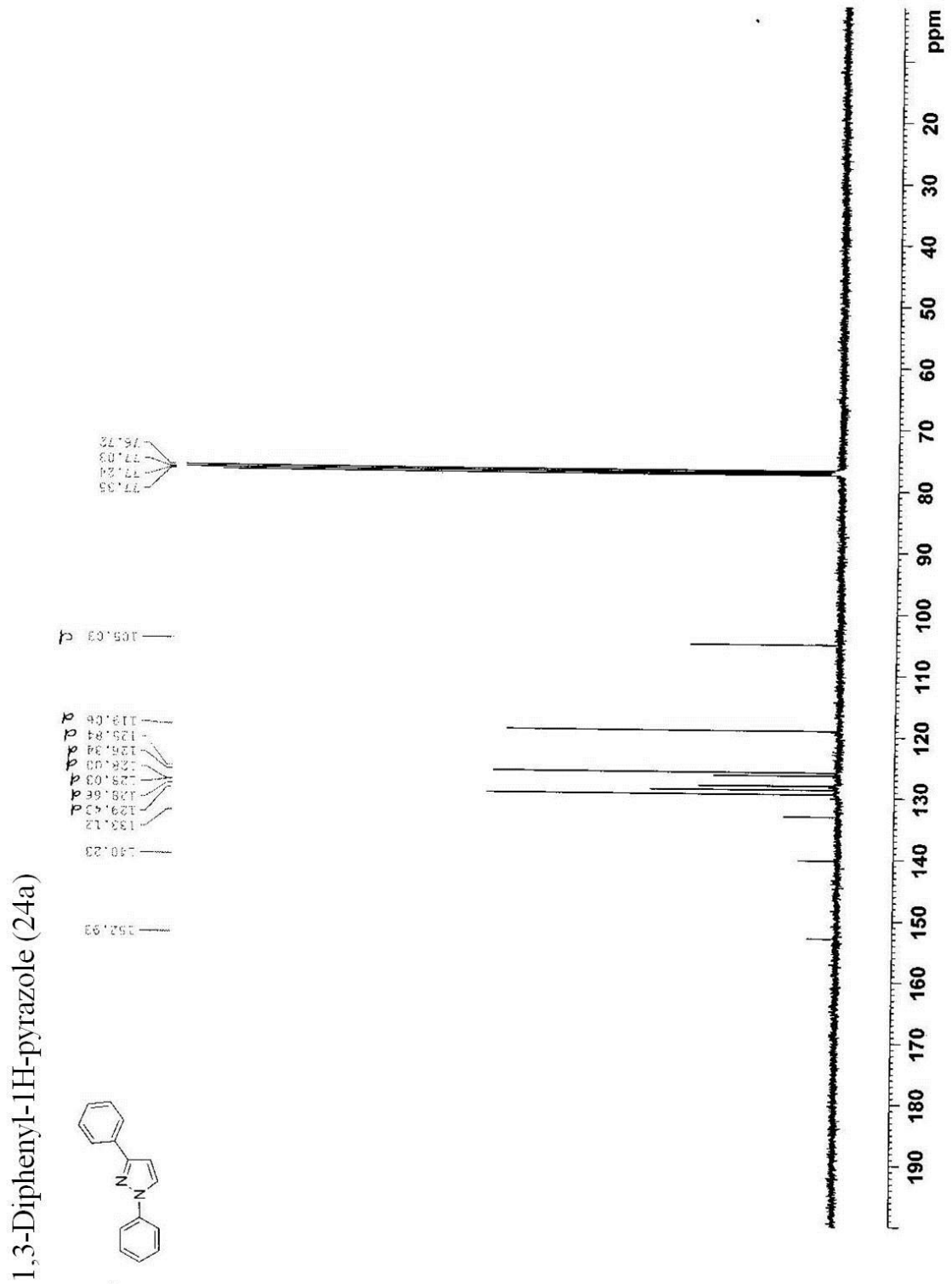
5.6. Selected NMR spectra

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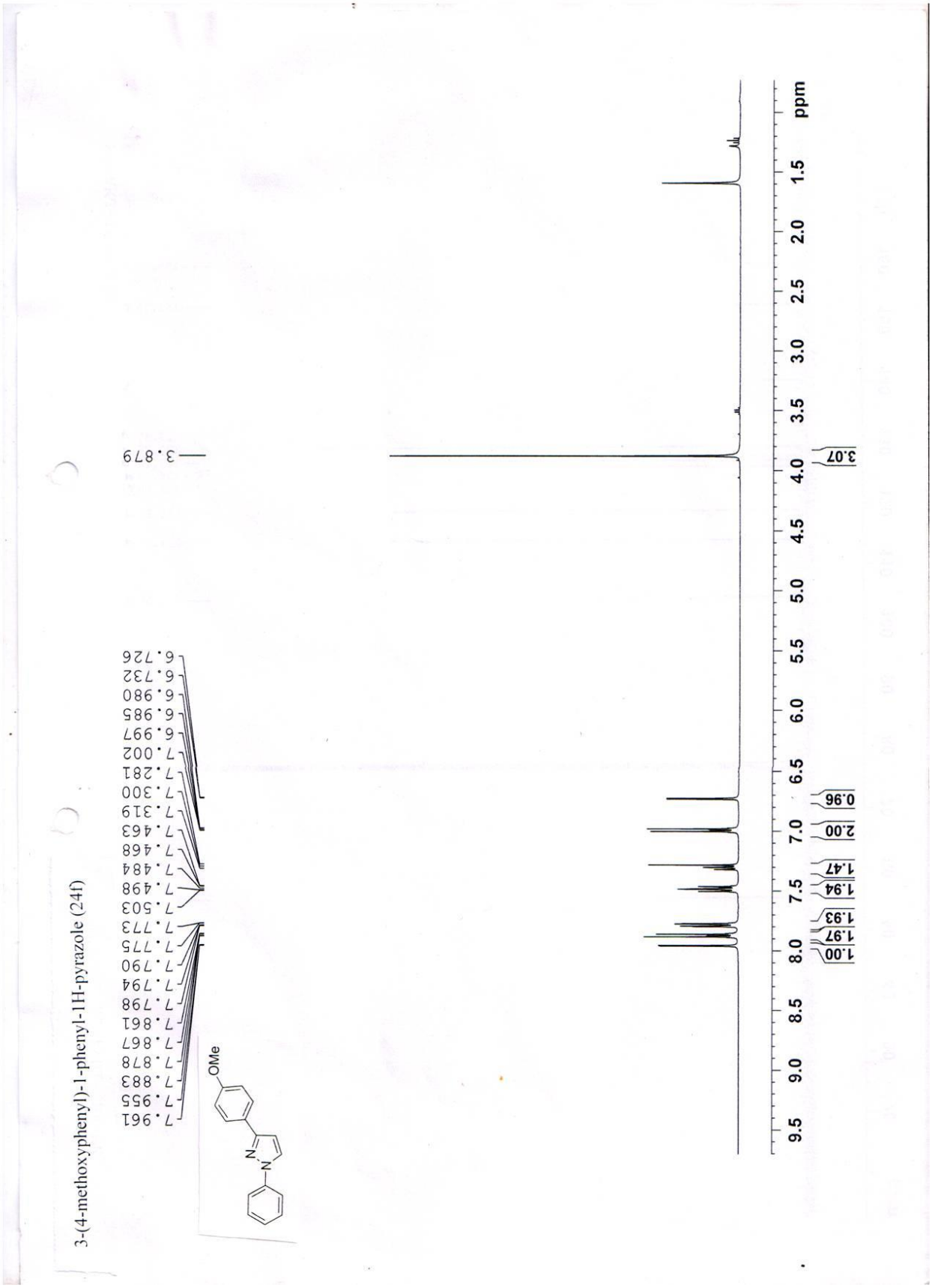
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7.861
7.798
7.794
7.790
7.775
7.773
7.503
7.498
7.484
7.468
7.463
7.319
7.300
7.281
7.002
6.997
6.985
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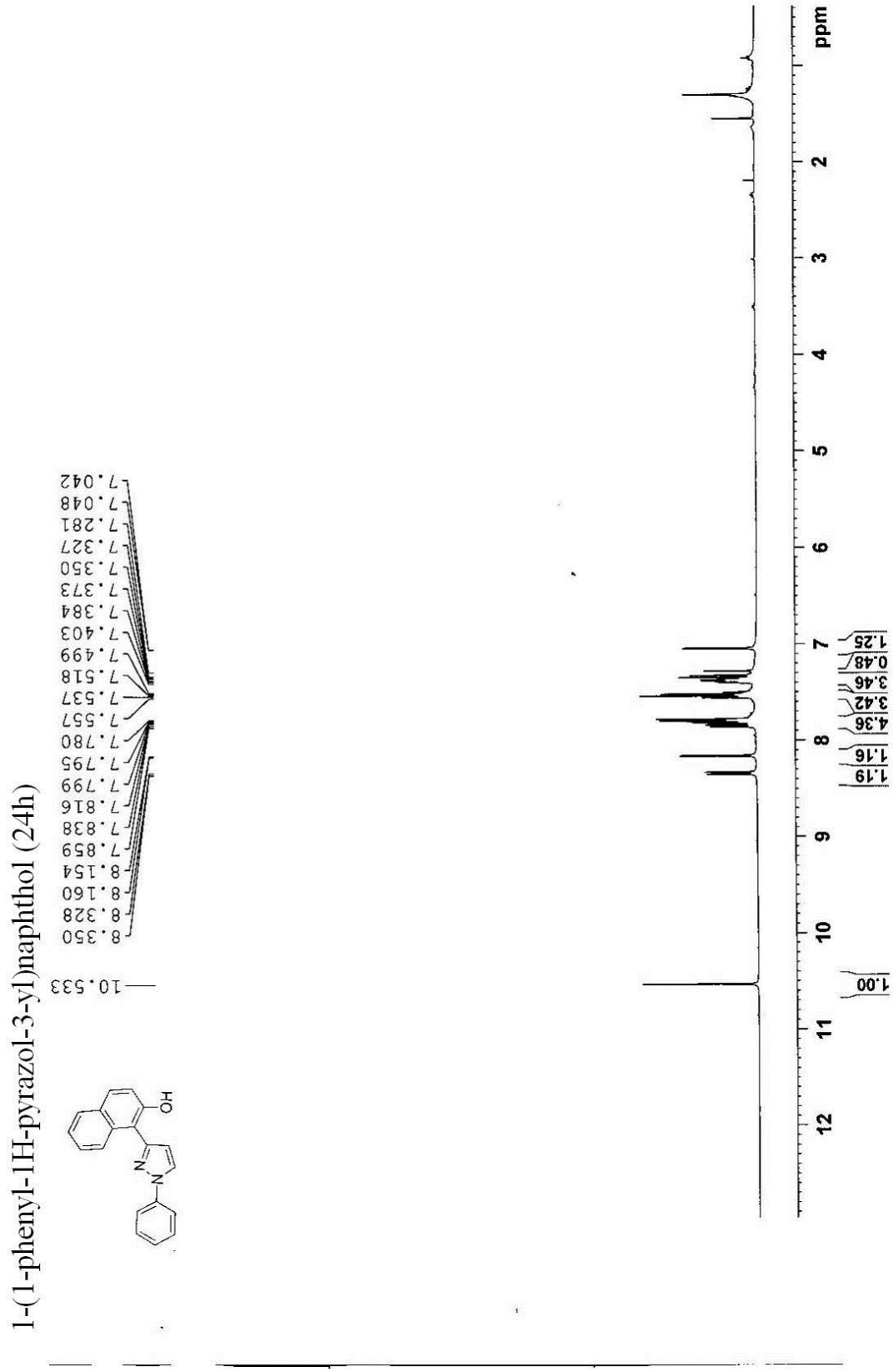
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7.816
7.799
7.795
7.780
7.557
7.537
7.518
7.499
7.403
7.384
7.373
7.350
7.327
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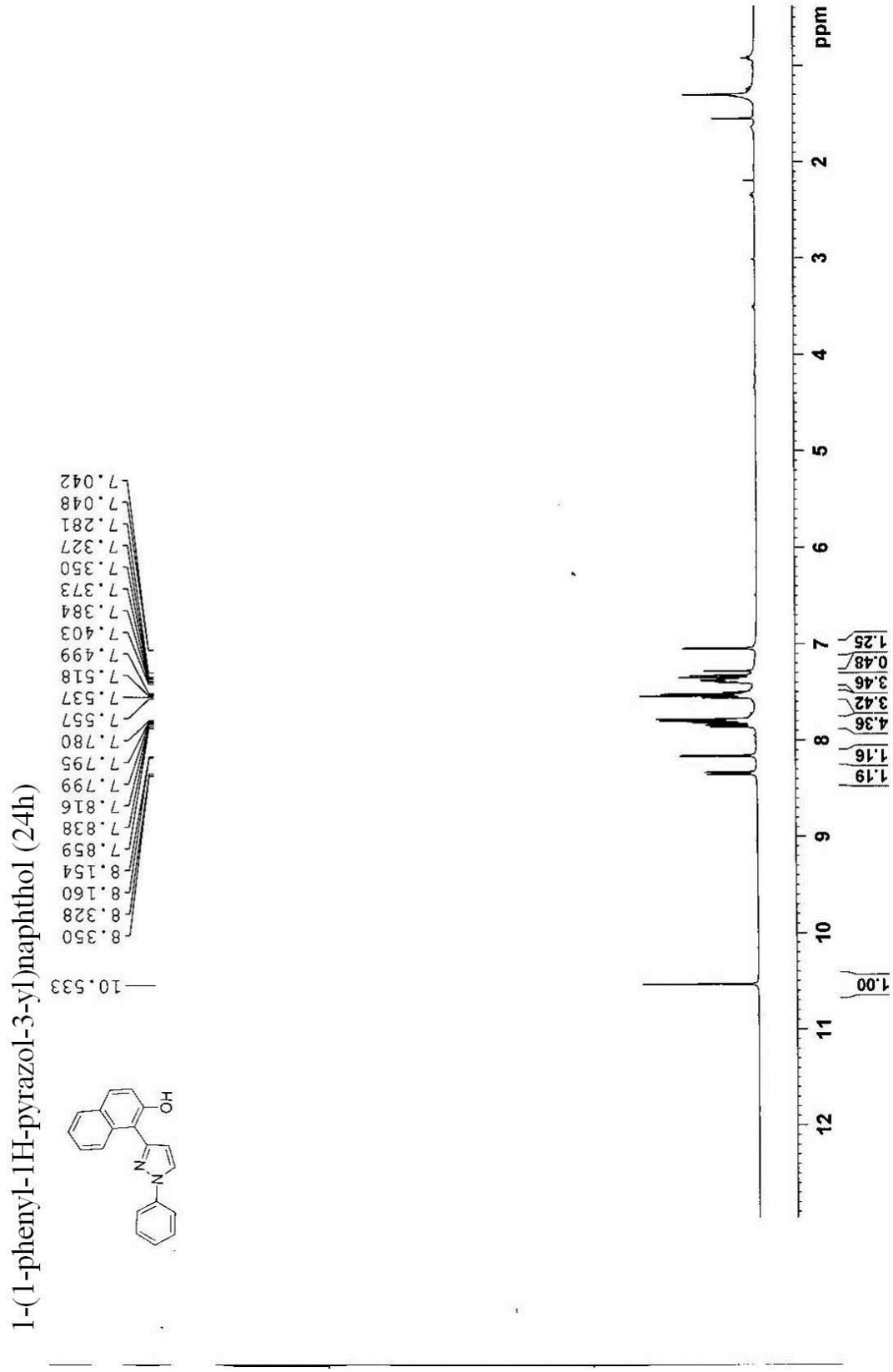
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7.799
7.795
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7.537
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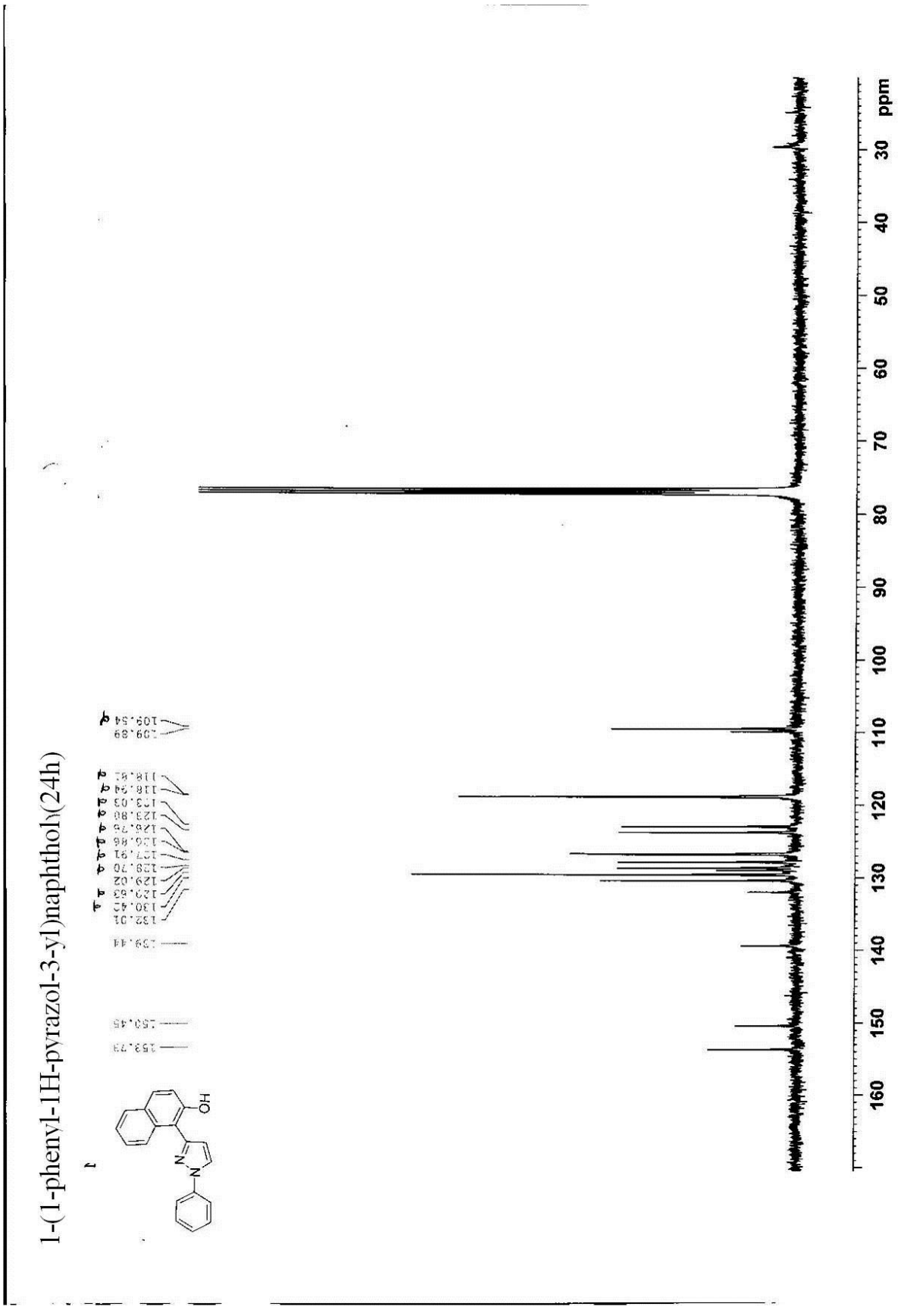
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ppm
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40
50
60
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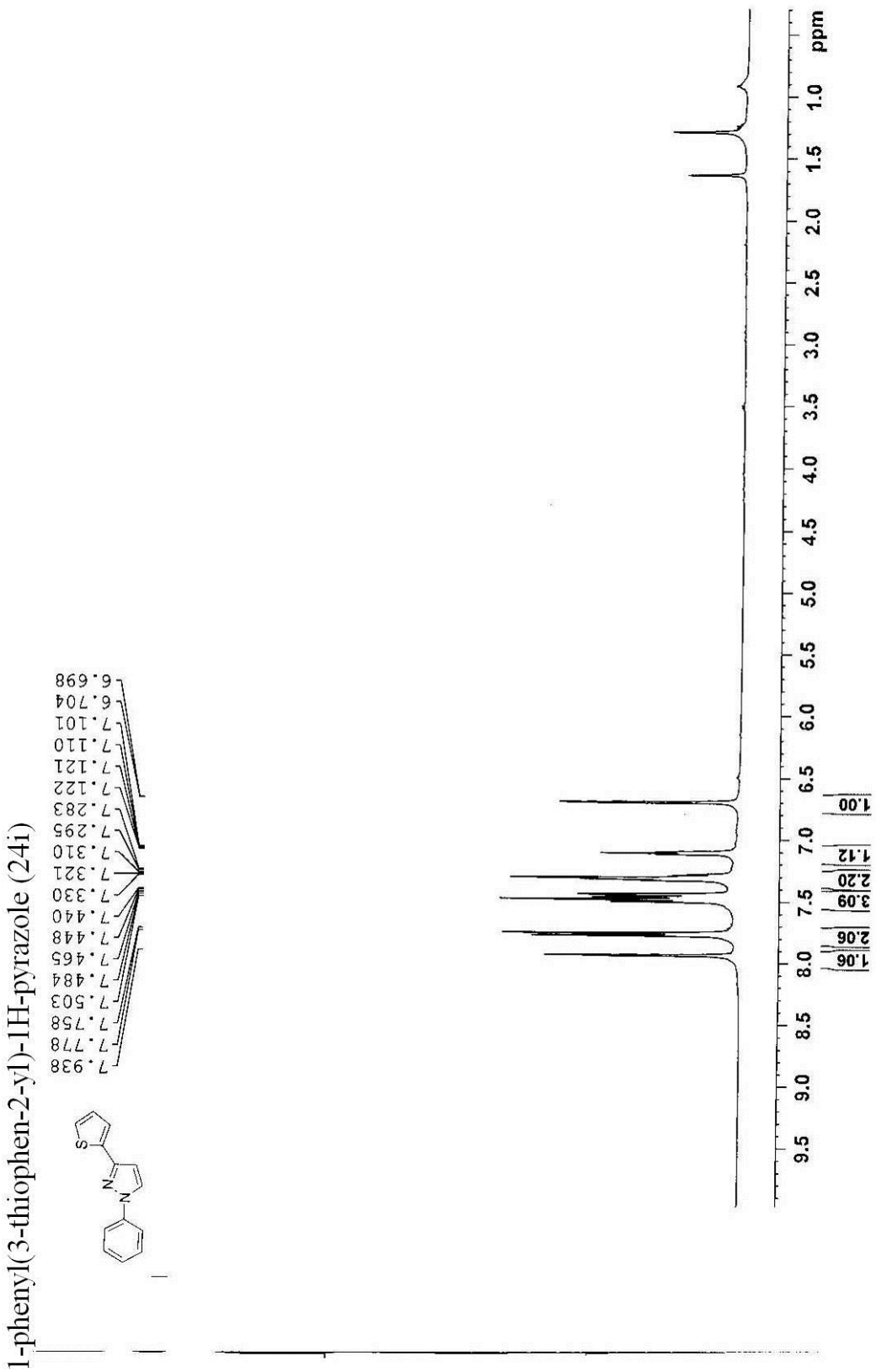
80
90
100
110
120
130
140
150
160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7.484
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7.321
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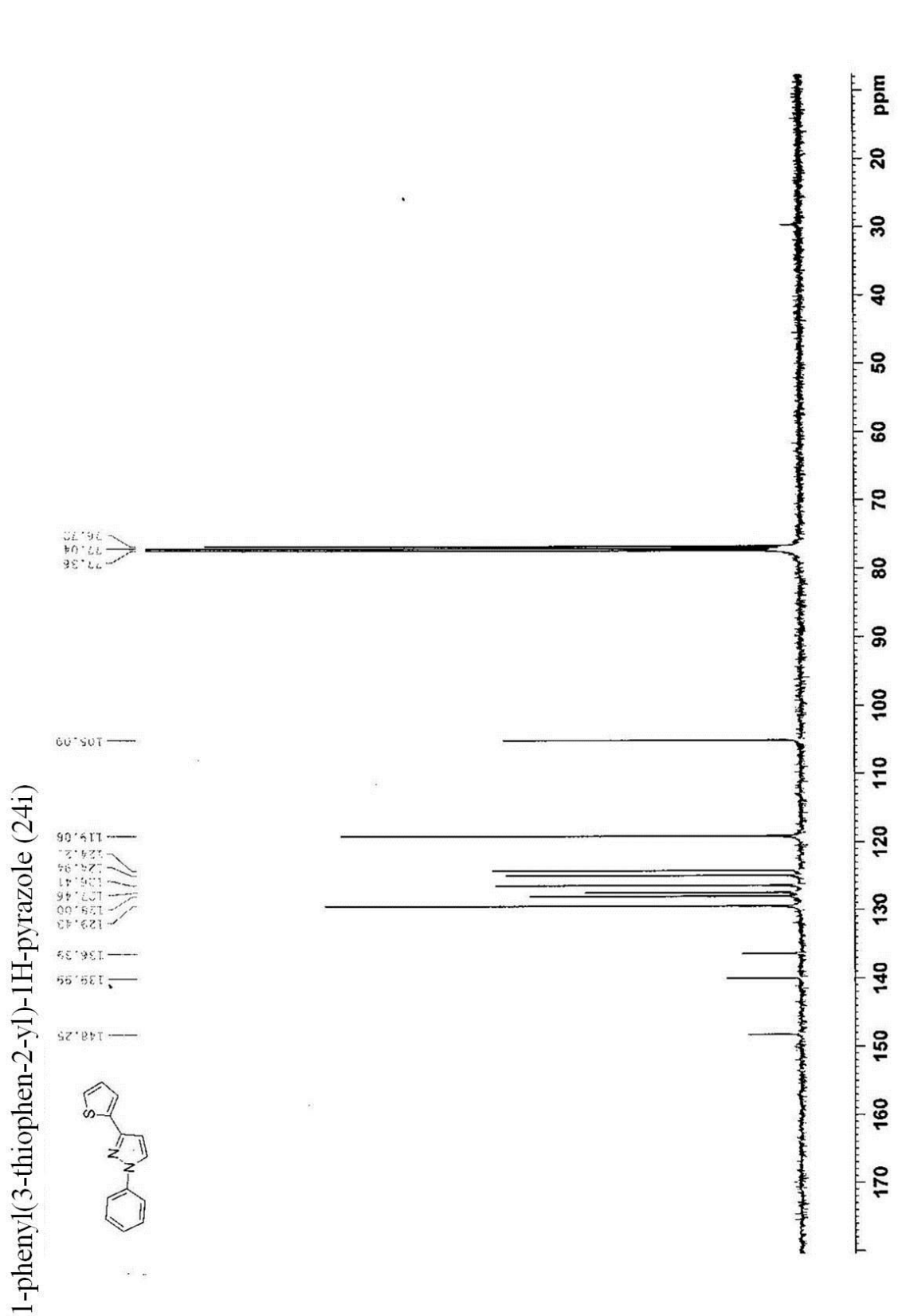
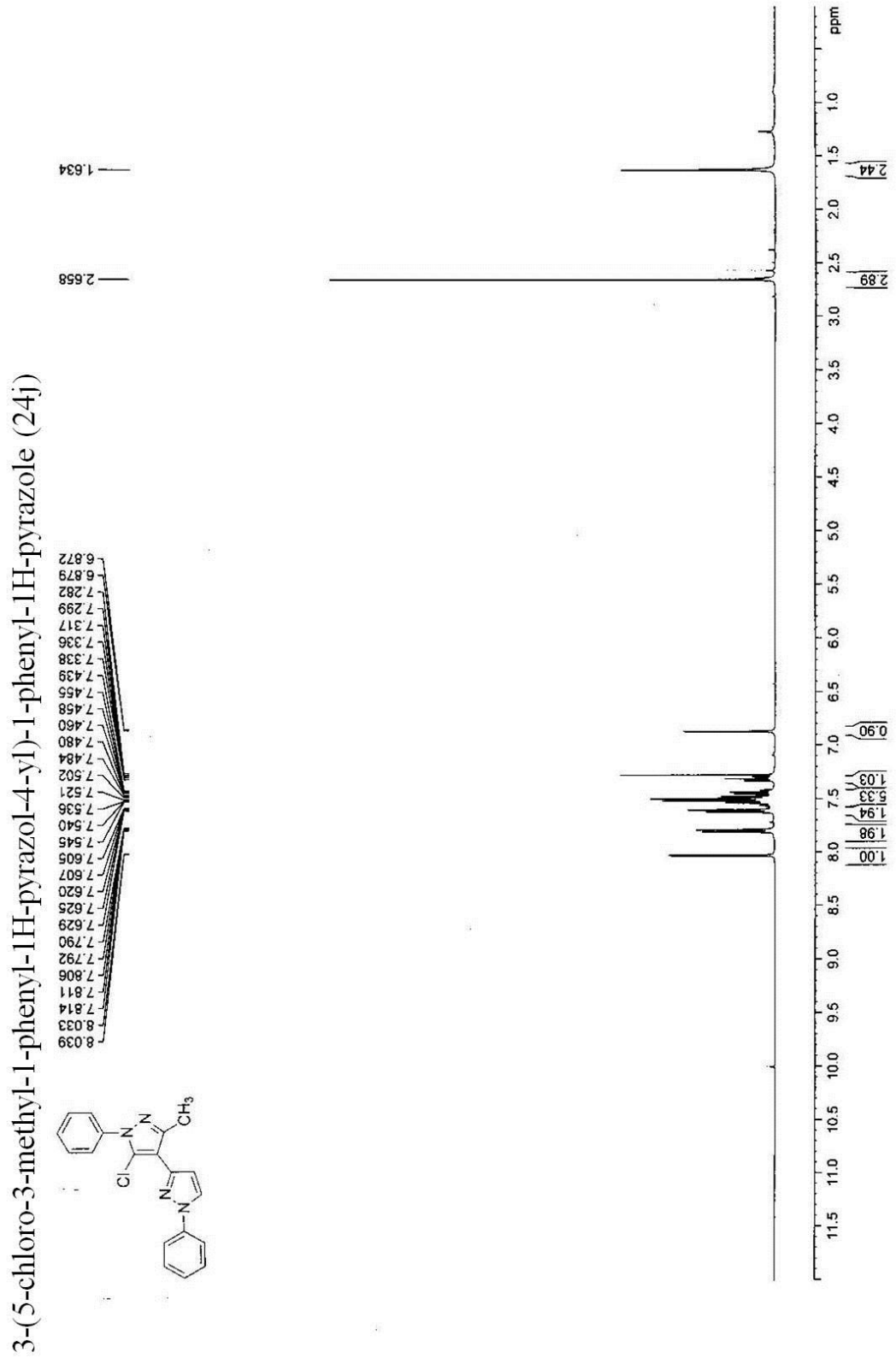
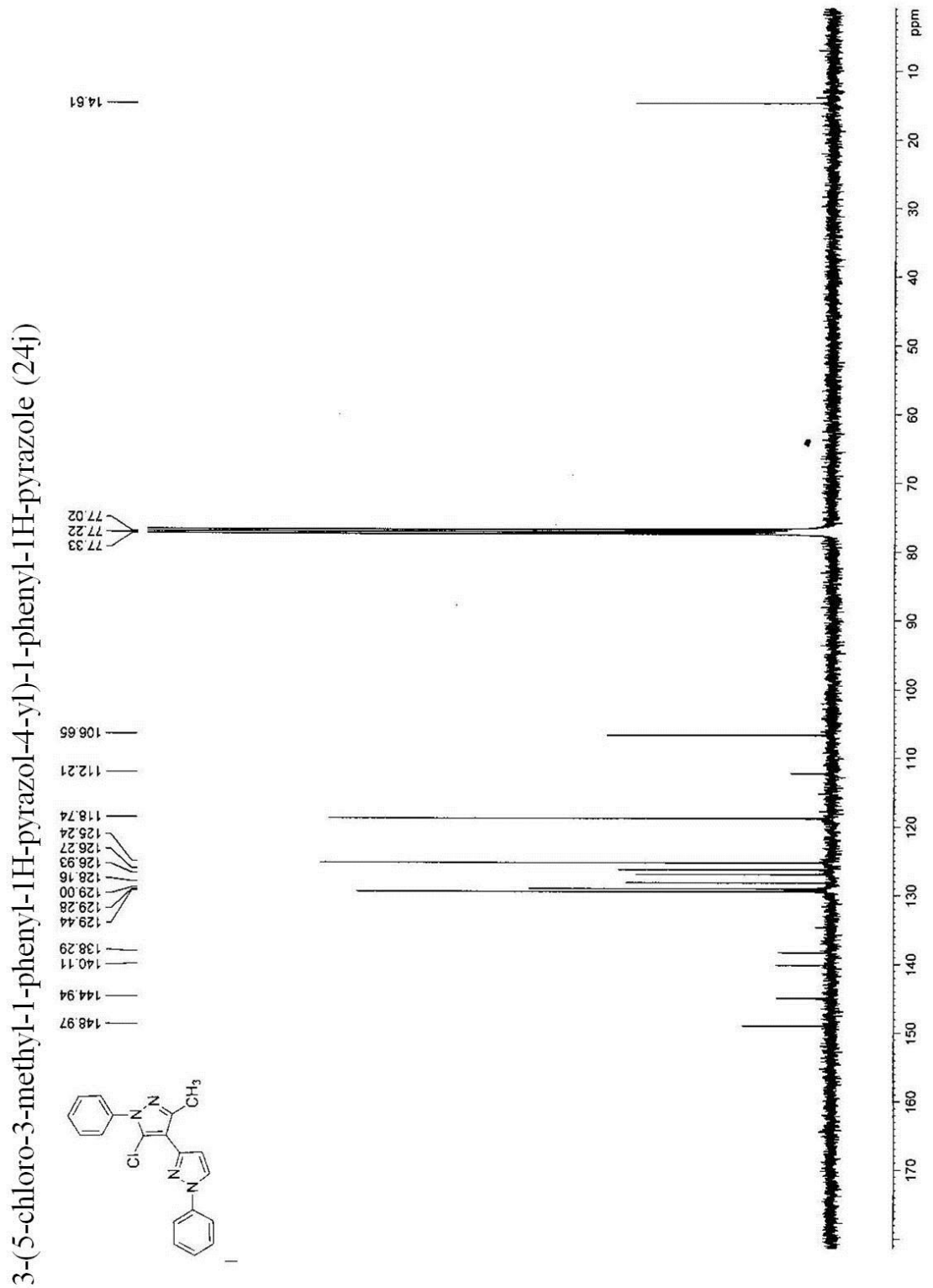
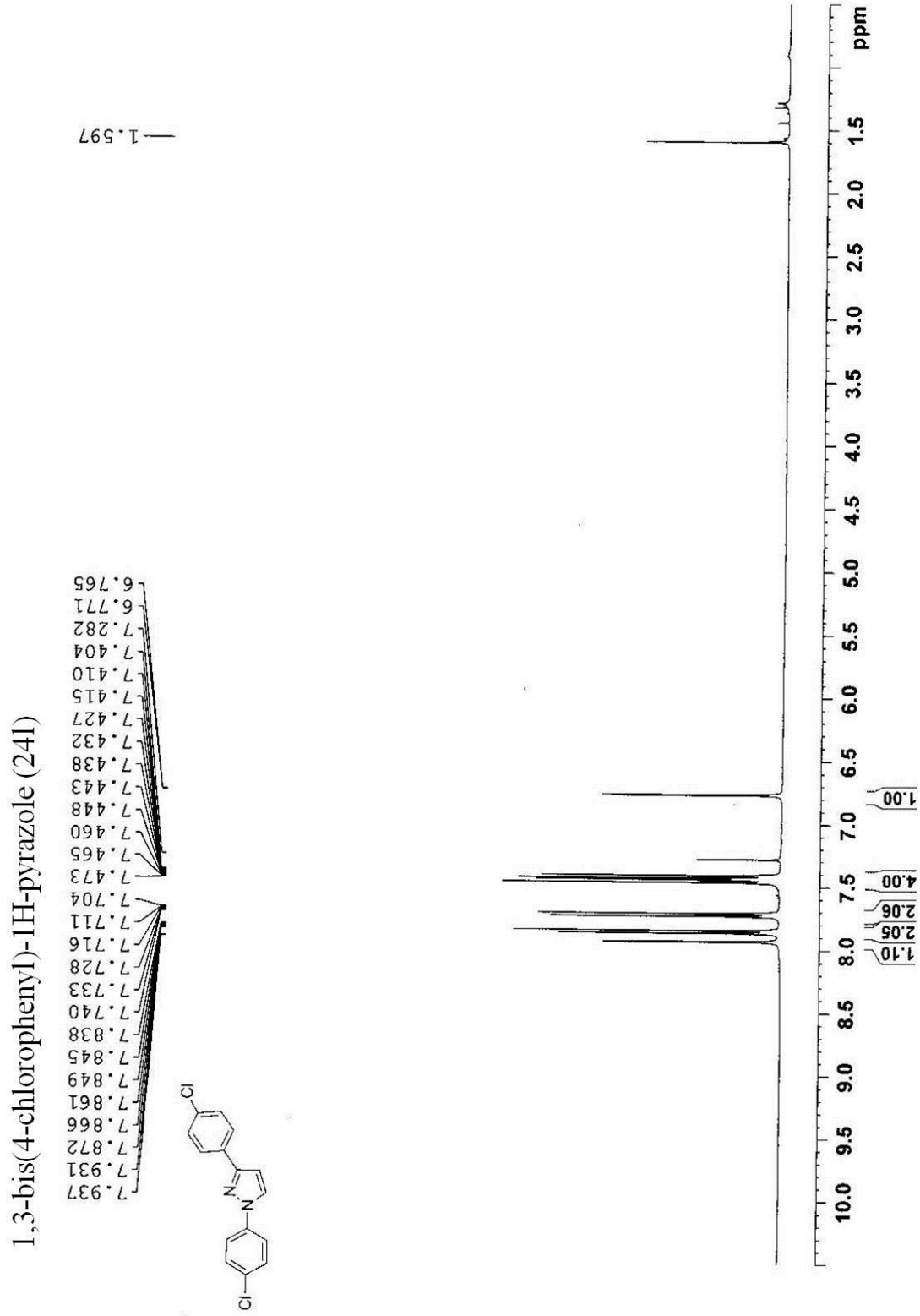
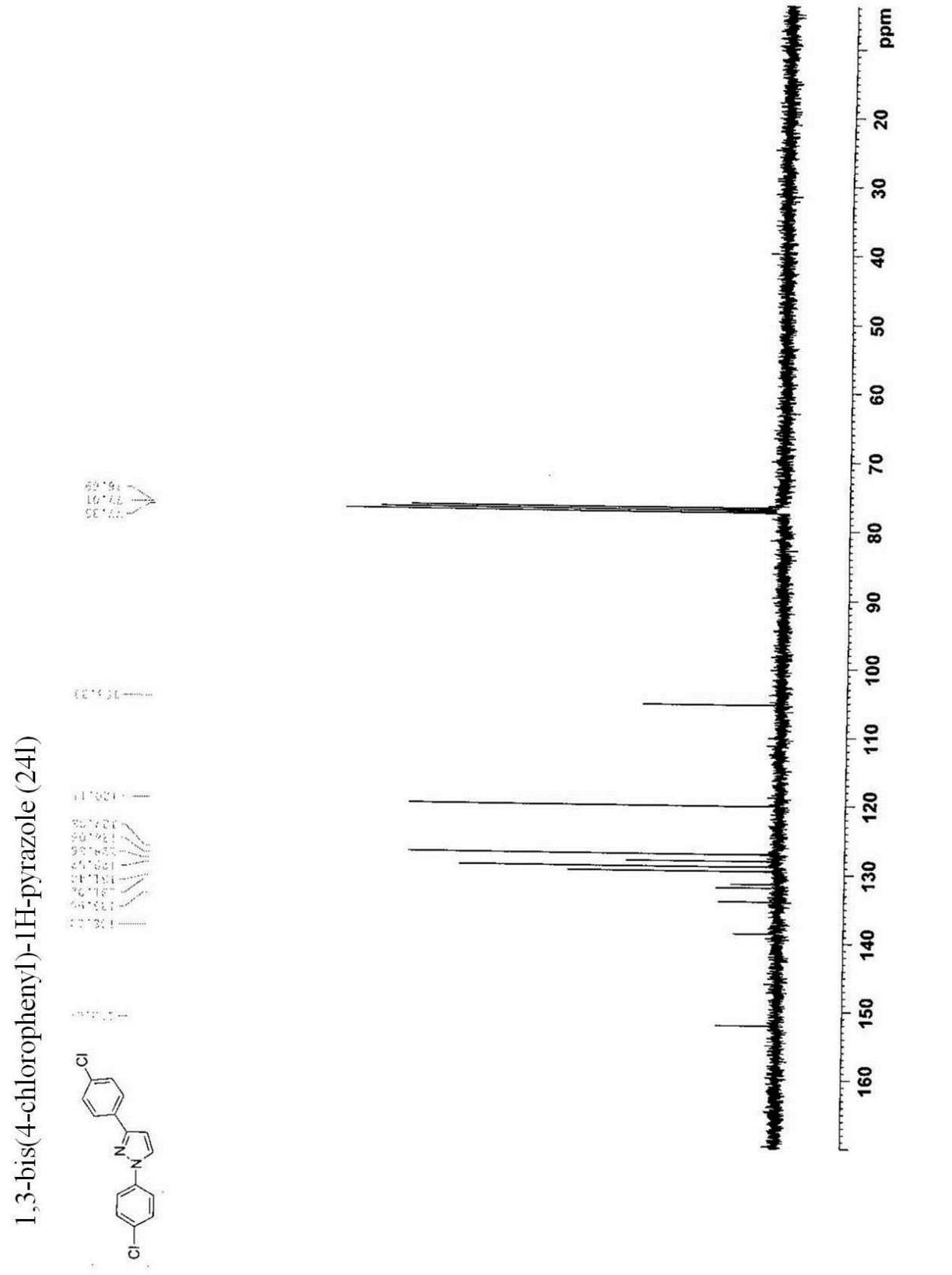
7.121
7.110
7.101
6.704
6.698
S
N
N
ppm
1.00
1.12
2.20
3.09
2.06
1.06

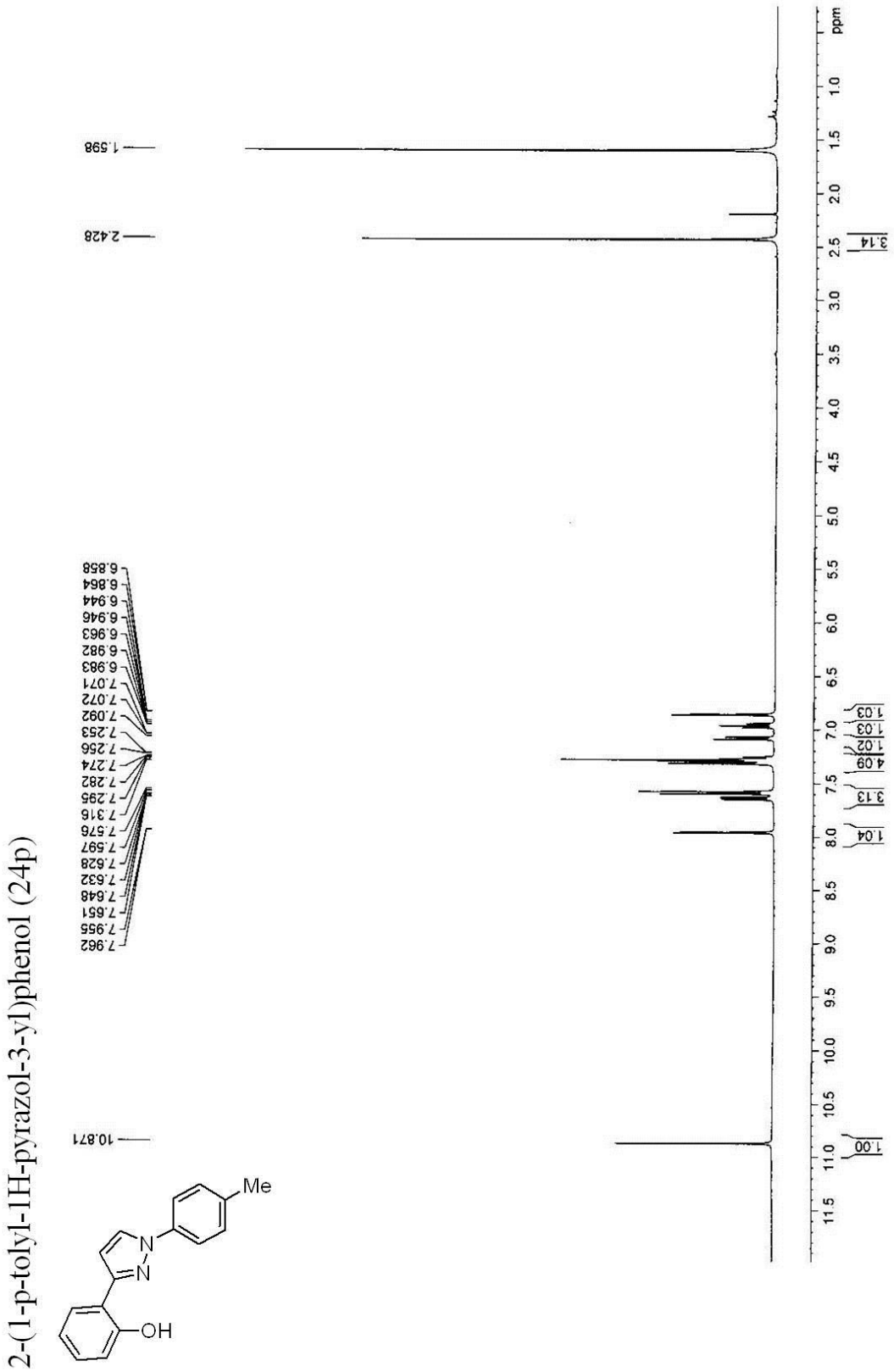

1-phenyl(3-thiophen-2-yl)-1H-pyrazole (24i)
148.25
139.99
136.39
129.43
129.00
127.46
126.41
124.94
124.12
119.06
105.09
77.36
77.04
76.72
S
N
N
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

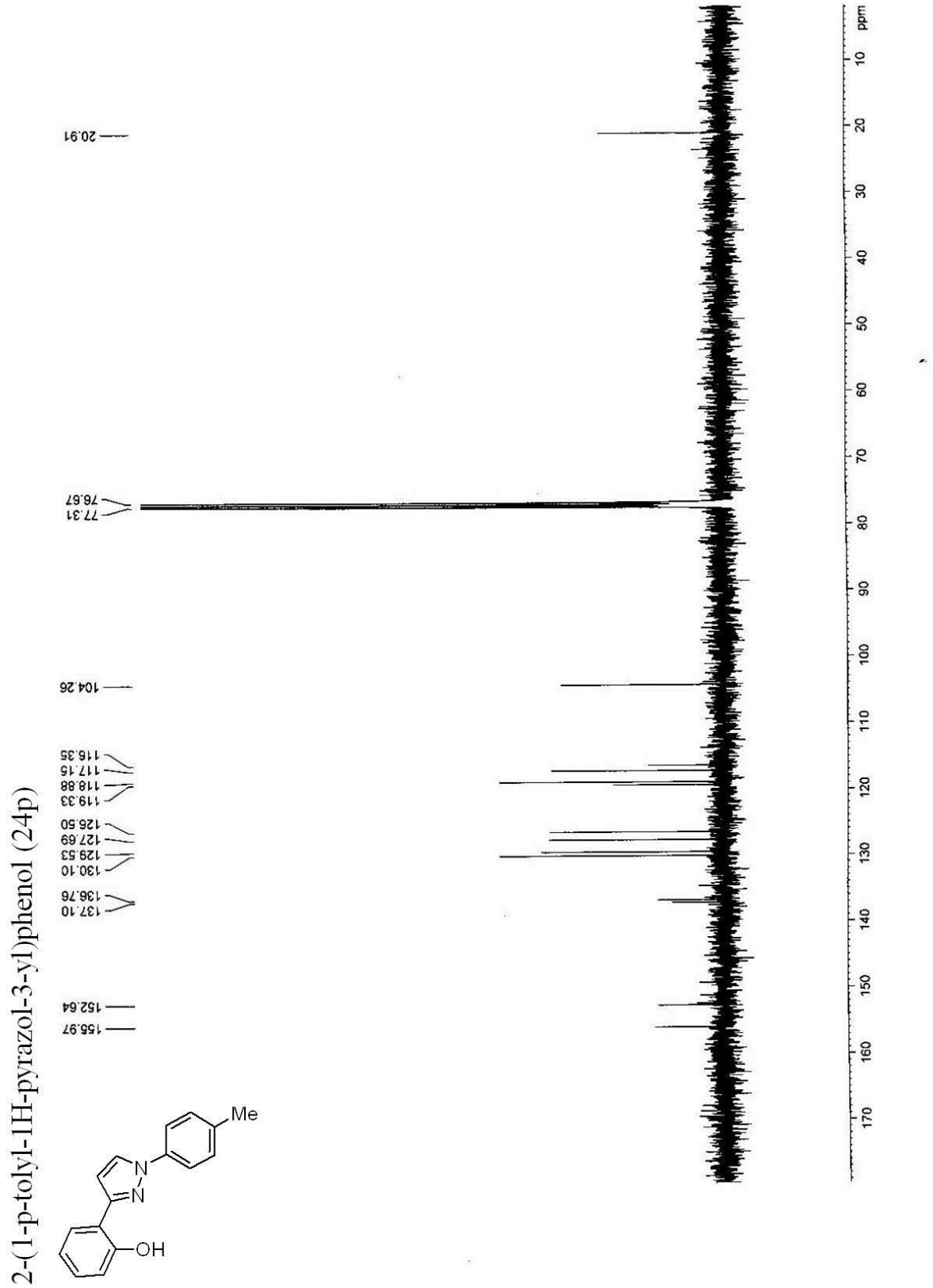

3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazole (24j)
1.634
2.658
8.039
8.033
7.814
7.811
7.806
7.792
7.790
7.629
7.625
7.620
7.607
7.605
7.545
7.540
7.536
7.521
7.502
7.484
7.480
7.460
7.458
7.455
7.439
7.338
7.336
7.317
7.299
7.282
6.879
6.872
Cl
CH3
N
N
N
N
ppm
2.44
2.89
0.90
1.03
5.33
1.94
1.98
1.00

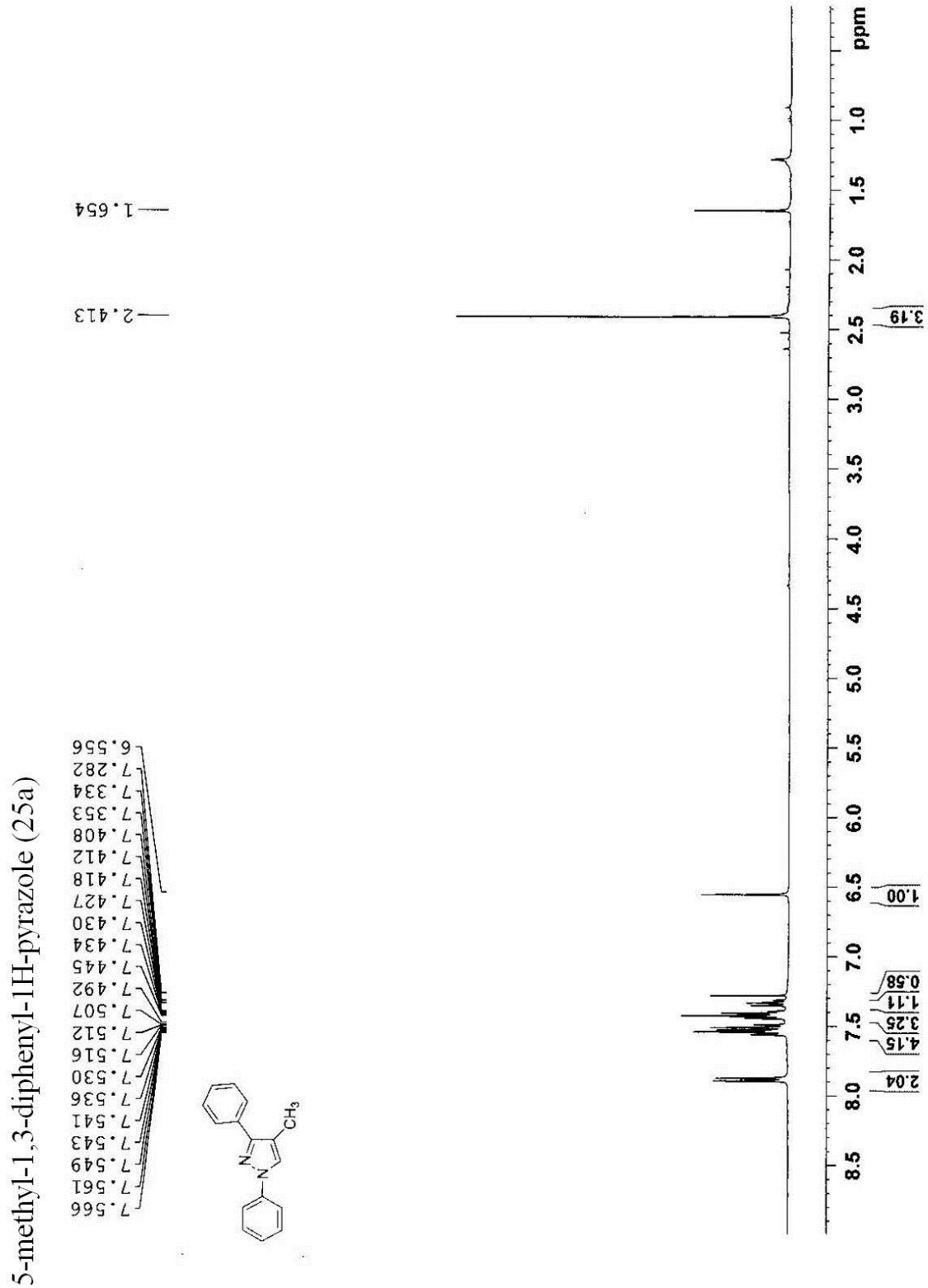

3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenyl-1H-pyrazole (24j)
14.61
77.33
77.22
77.02
106.65
112.21
118.74
125.24
126.27
126.93
128.16
129.00
129.28
129.44
138.29
140.11
144.94
148.97
Cl
CH3
N
N
N
N
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

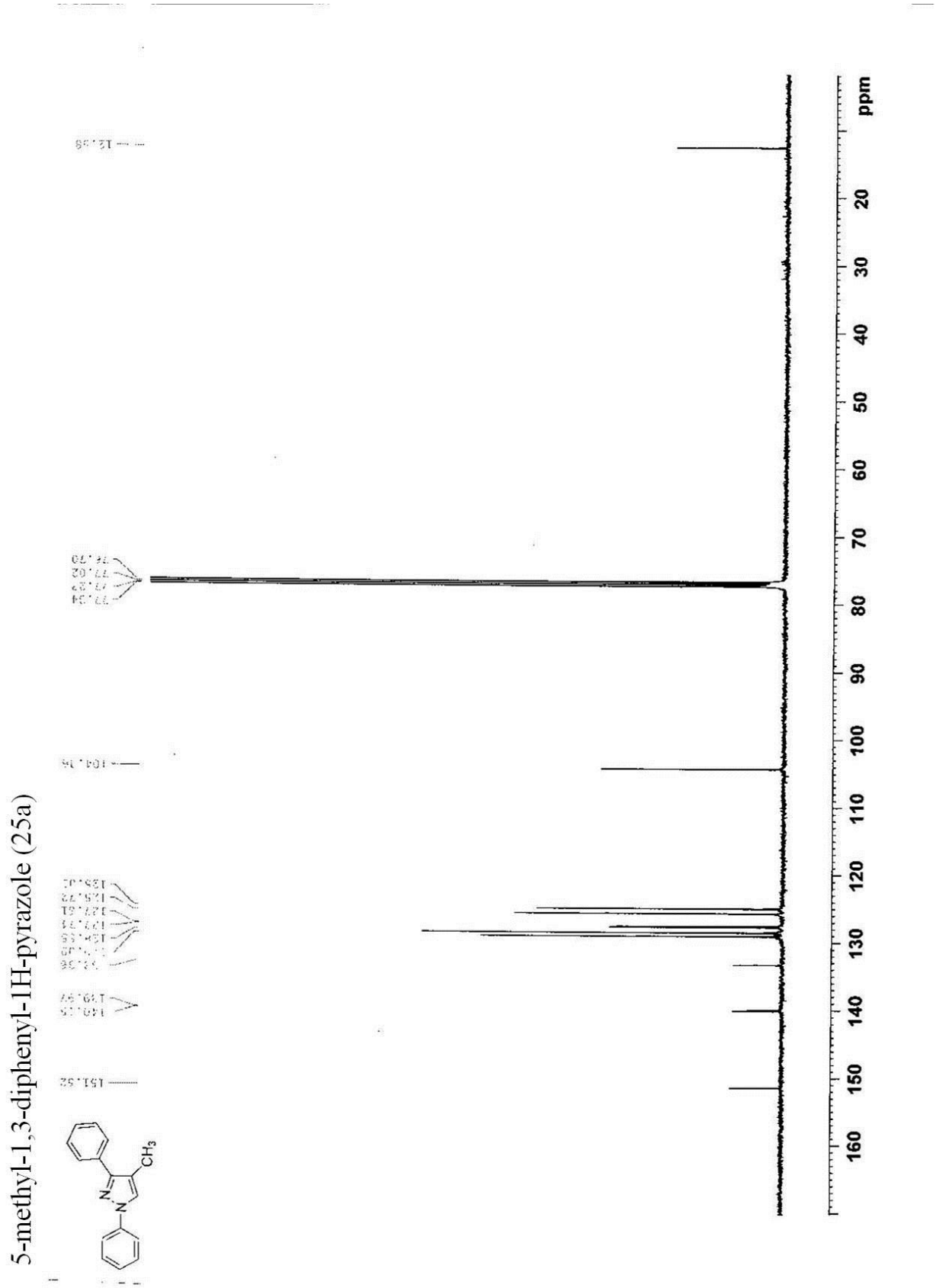

1,3-bis(4-chlorophenyl)-1H-pyrazole (24l)
1.597
7.937
7.931
7.872
7.866
7.861
7.849
7.845
7.838
7.740
7.733
7.728
7.716
7.711
7.704
7.473
7.465
7.460
7.448
7.443
7.438
7.432
7.427
7.415
7.410
7.404
7.282
6.771
6.765
Cl
N
N
Cl
ppm
1.00
4.00
2.06
2.05
1.10

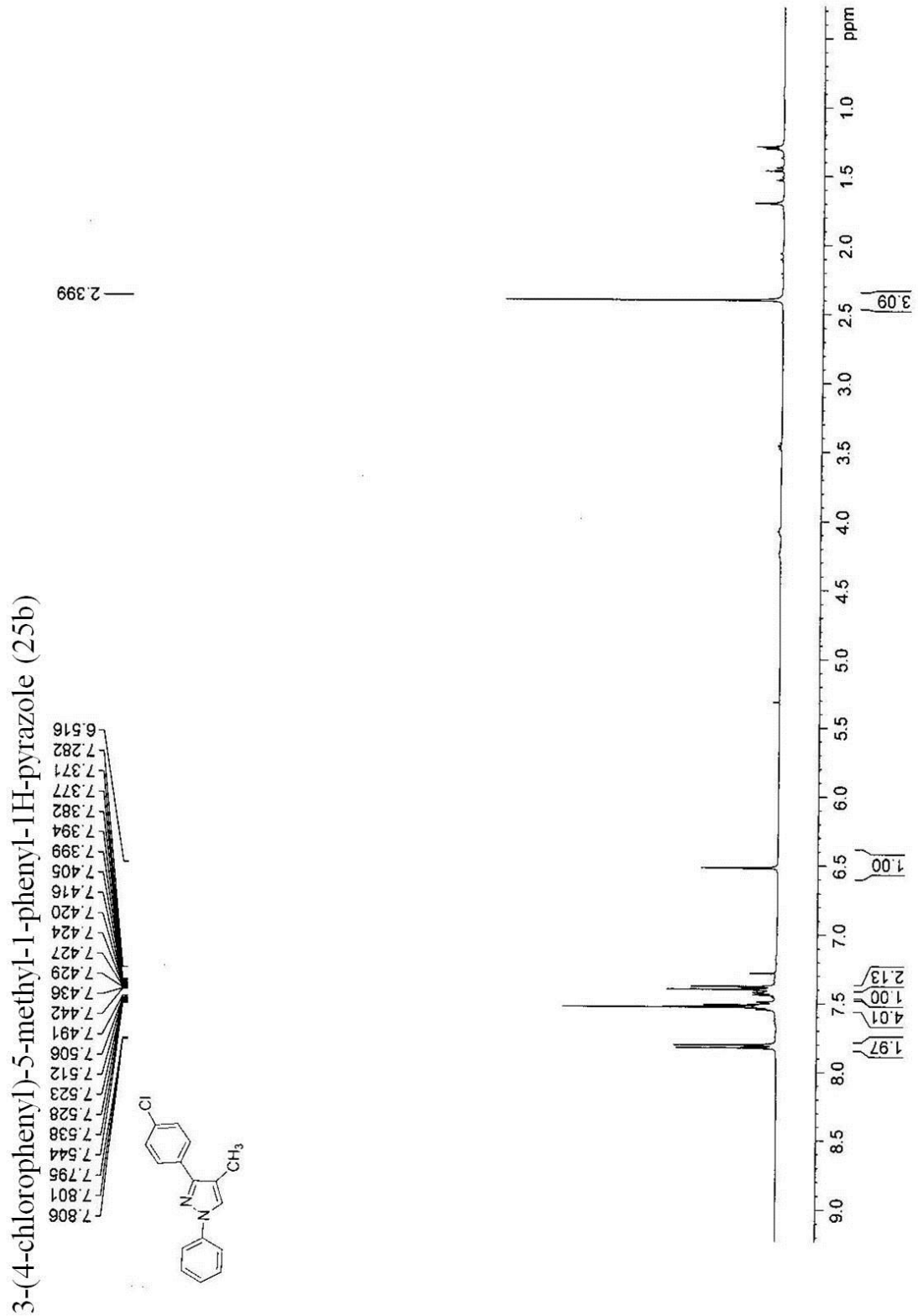

1,3-bis(4-chlorophenyl)-1H-pyrazole (24l)
Cl
N
N
Cl
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

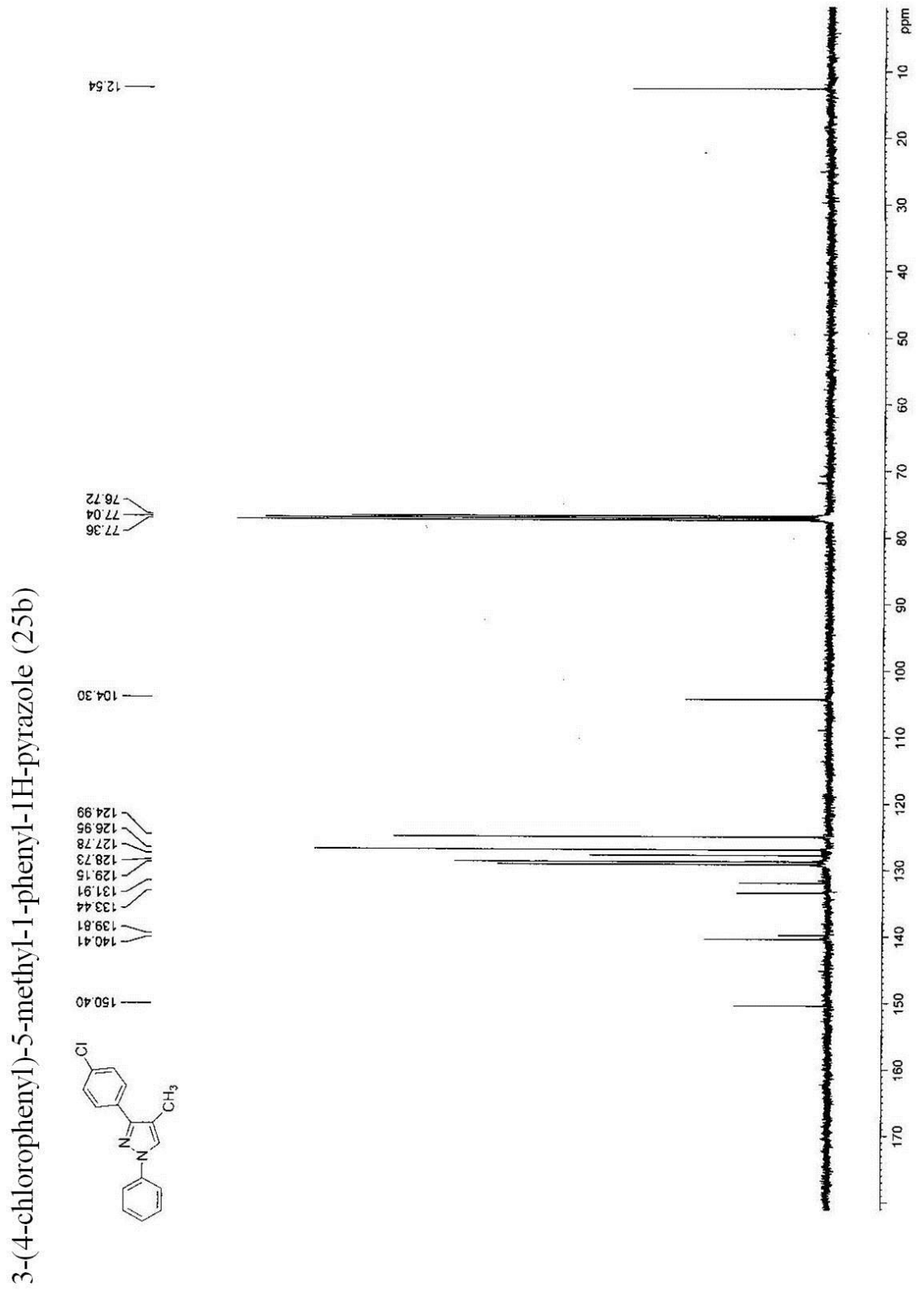

2-(1-p-tolyl-1H-pyrazol-3-yl)phenol (24p)
1.598
2.428
6.858
6.864
6.944
6.946
6.963
6.982
6.983
7.071
7.072
7.092
7.253
7.256
7.274
7.282
7.295
7.316
7.576
7.597
7.628
7.632
7.648
7.651
7.955
7.962
10.871
Me
N
N
OH
ppm
3.14
1.03
1.03
1.02
4.09
3.13
1.04
1.00

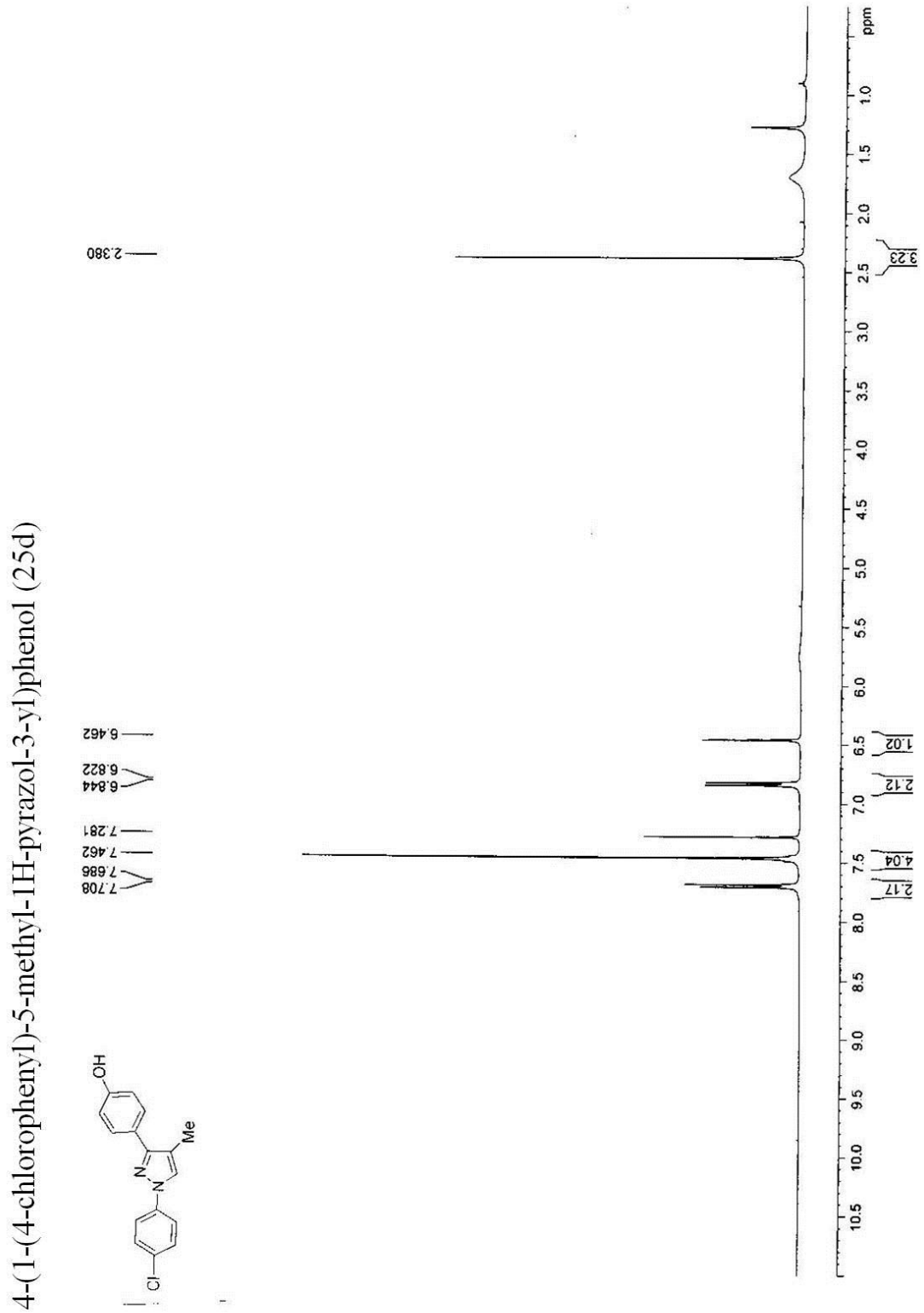

2-(1-p-tolyl-1H-pyrazol-3-yl)phenol (24p)
20.91
76.67
77.31
104.26
116.35
117.15
118.88
119.33
126.50
127.69
129.53
130.10
136.76
137.10
152.64
155.97
Me
N
N
OH
ppm

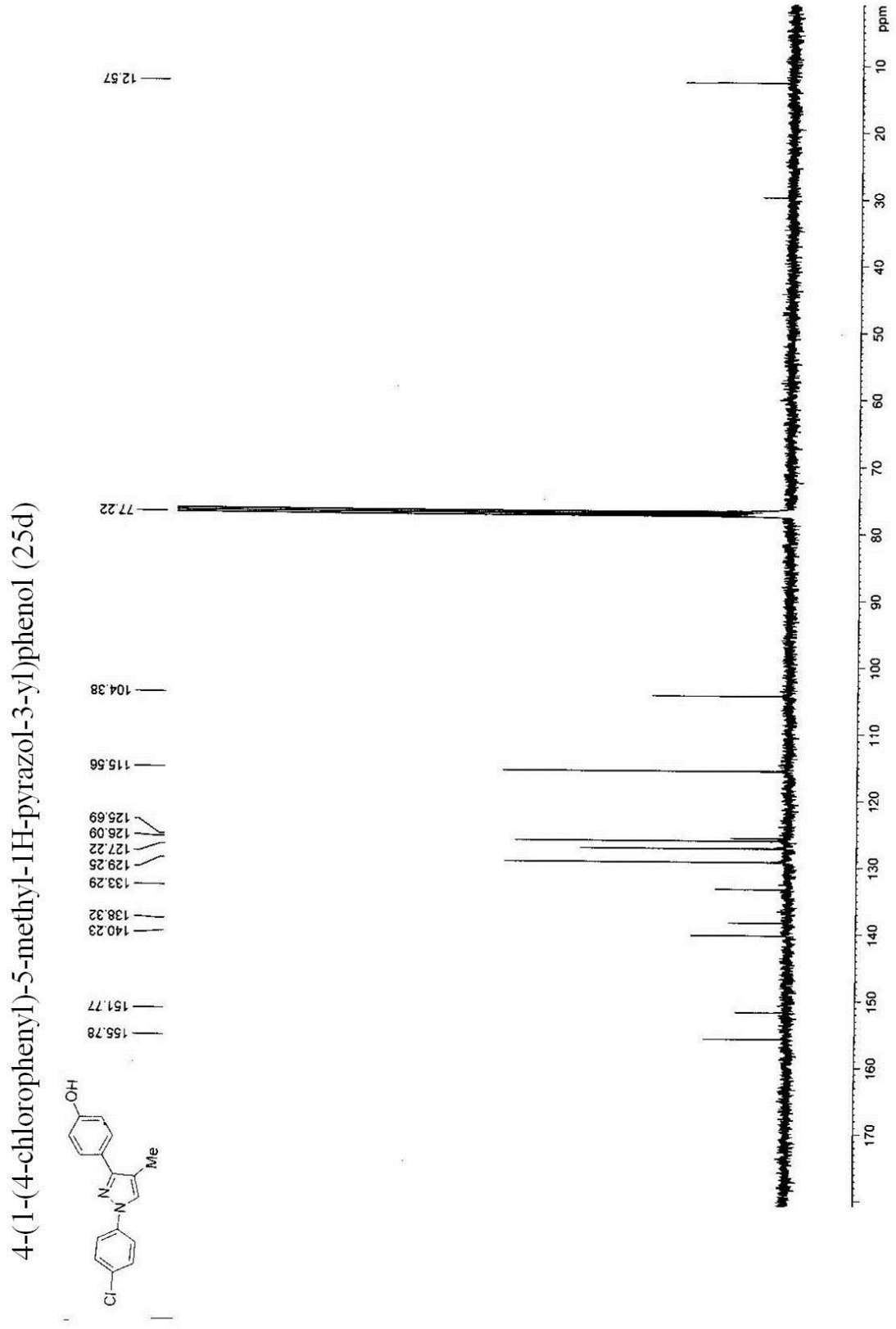

5-methyl-1,3-diphenyl-1H-pyrazole (25a)
6.556
7.282
7.334
7.353
7.408
7.412
7.418
7.427
7.430
7.434
7.445
7.492
7.507
7.512
7.516
7.530
7.536
7.541
7.543
7.549
7.561
7.566
2.413
1.654
CH3
N
N
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
3.19
1.00
0.58
1.11
3.25
4.15
2.04

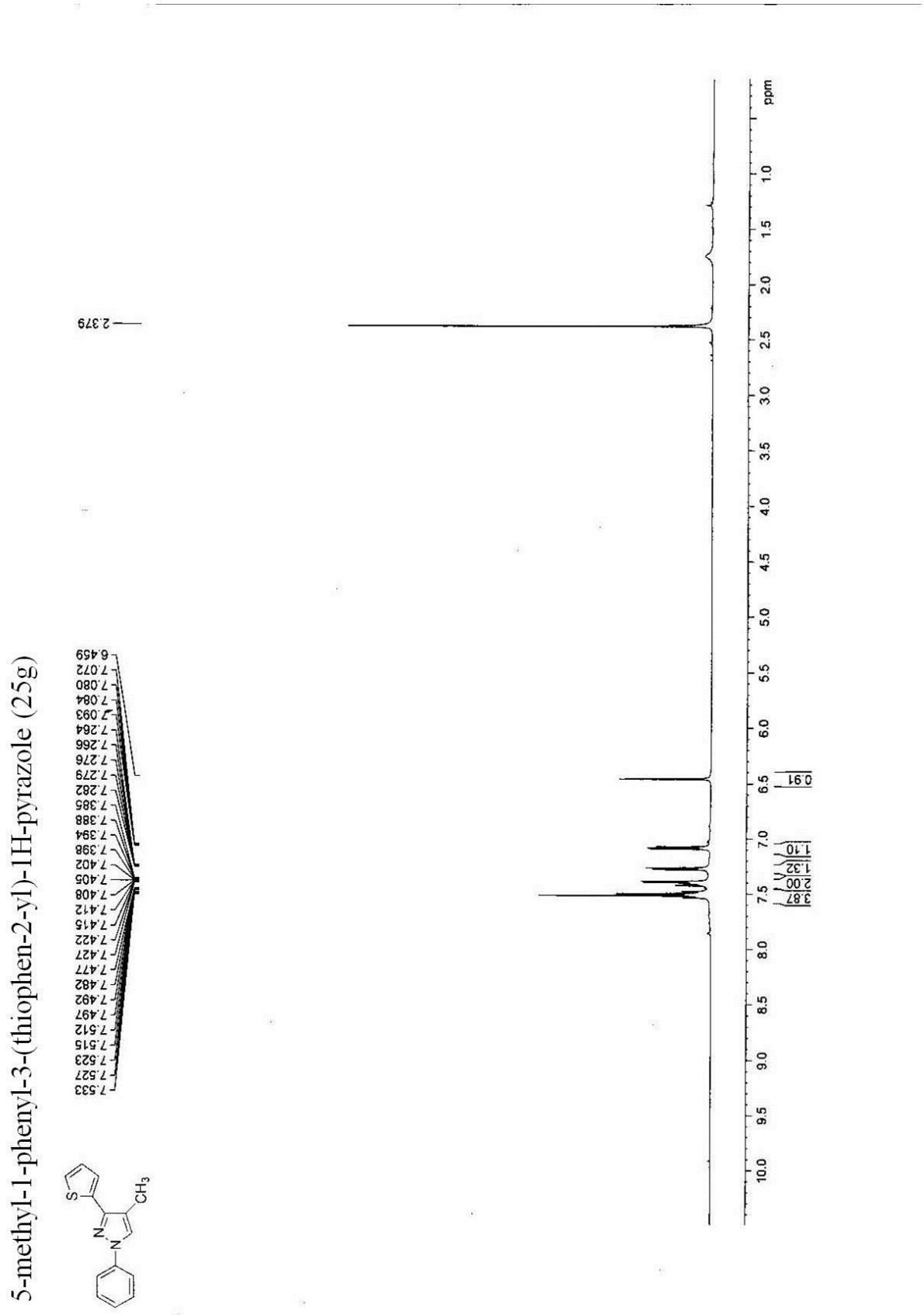

5-methyl-1,3-diphenyl-1H-pyrazole (25a)
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
CH3
N
N

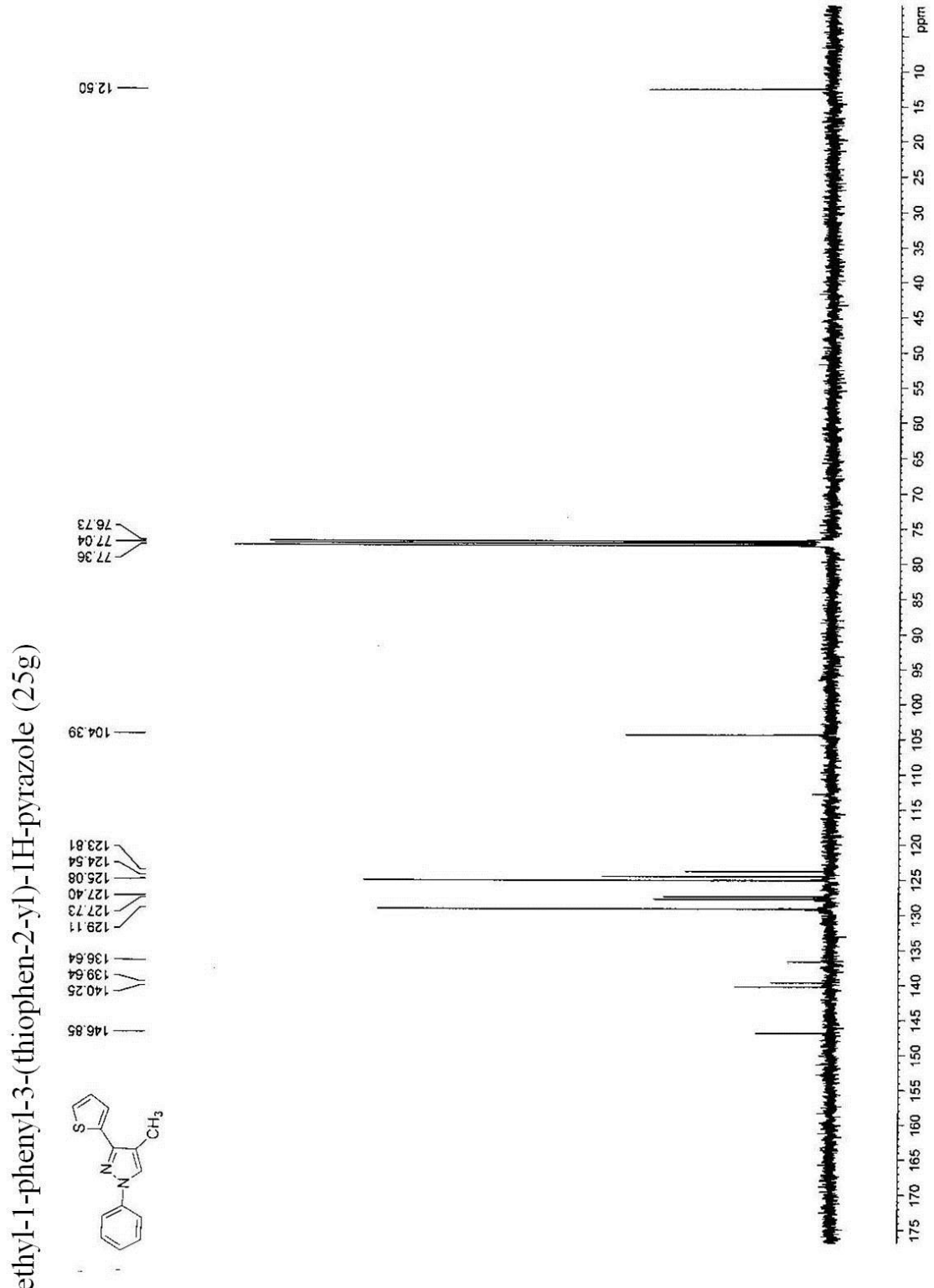

3-(4-chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole (25b)
6.516
7.282
7.371
7.377
7.382
7.394
7.399
7.405
7.416
7.420
7.424
7.427
7.429
7.436
7.442
7.491
7.506
7.512
7.523
7.528
7.538
7.544
7.795
7.801
7.806
2.399
Cl
CH3
N
N
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
3.09
1.00
2.13
1.00
4.01
1.97


3-(4-chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole (25b)
12.54
76.72
77.04
77.36
104.30
124.99
126.95
127.78
128.73
129.15
131.91
133.44
139.81
140.41
150.40
Cl
CH3
N
N
ppm


4-(1-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl)phenol (25d)
2.380
6.462
6.844
6.822
7.281
7.462
7.686
7.708
3.23
1.02
2.12
4.04
2.17
ppm
OH
Me
N
N
Cl


4-(1-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl)phenol (25d)
12.57
77.22
104.38
115.56
125.69
126.09
127.22
129.25
133.29
138.32
140.23
151.77
155.78
OH
Me
N
N
Cl
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170


5-methyl-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (25g)
2.379
7.533
7.527
7.523
7.515
7.512
7.497
7.492
7.482
7.477
7.427
7.422
7.415
7.412
7.408
7.405
7.402
7.398
7.394
7.388
7.385
7.282
7.279
7.276
7.266
7.264
7.093
7.084
7.080
7.072
6.459
S
N
N
CH3
0.91
1.10
1.32
2.00
3.87
ppm


5-methyl-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (25g)
12.50
76.73
77.04
77.36
104.39
123.81
124.54
125.08
127.40
127.73
129.11
136.64
139.64
140.25
146.85
S
N
N
CH3
ppm

List of Publications

1. Niranjan Panda,* Ashis Kumar Jena and Sasmita Mohapatra, Ligand-free Fe-Cu Cocatalyzed Cross-Coupling of Terminal Alkynes with Aryl Halides, *Chem. Lett.* **2011**, *40*, 956.
2. Niranjan Panda,*Ashis Kumar Jena, Sasmita Mohapatra and Smruti Ranjan Rout, Copper ferrite nanoparticle-mediated N-arylation of heterocycles: a ligand-free reaction, *Tetrahedron Lett.* **2011**, *52*, 1924.
   (Highlighted in *Synfact*, **2011**, 686.)
3. Niranjan Panda,* Ashis Kumar Jena and Sasmita Mohapatra*, Heterogeneous magnetic catalyst for S-arylation reactions, *Appl. Catal. A: Gen.* **2012**, *433-434*, 258.
4. Niranjan Panda* and Ashis Kumar Jena, Fe-Catalyzed One-Pot Synthesis of 1,3-Di and 1,3,5-Trisubstituted Pyrazoles from Hydrazones and Vicinal Diols, *J. Org. Chem.* **2012**, *77*, 9401.
   (Highlighted in *Synfact*, **2013**, 28.)
5. Niranjan Panda,* Ashis K. Jena and M. Raghavender, Stereoselective Synthesis of Enamides by Palladium Catalyzed Coupling of Amides with Electron Deficient Olefins, *ACS Catalysis* **2012**, *2*, 539.
6. N. Panda,* S. Karmakar, A. K. Jena, Synthesis and Antibacterial Activity of some Novel Pyrazolopyridine Derivatives, *Chem. Heterocycl. Compd.* **2010**, *46* 1500.